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Annotation

Ph¹-POSITIVE ACUTE LEUKAEMIA AND CHRONIC GRANULOCYTIC LEUKAEMIA: ONE OR TWO DISEASES?

It is now accepted that Ph¹-positive chronic granulocytic leukaemia (CGL) is a clonal dircasc (Fialkow, 1974) of a pluripotent stem ccll, possibly a common precursor of mycloid and lymphoid cclls (Boggs, 1974; Janossy *et al*, 1976). The utilization of new cell marker tcchniqucs such as anti-ALL scrum (Greaves, 1975) and the enzymic terminal transferase (TdT) (McCaffrey *et al*, 1975; Sarin *et al*, 1976; Hoffbrand *et al*, 1977) havc improved the characterization of the cclls of blast crisis (BC) of CCL and made it possiblc to compare them with the blasts of other leukaemias, particularly acute lymphobiastic leukaemia (ALL), some of which havc now been found to bc Ph¹-positive without other features of CGL.

Blast cclls during the BC of CGL have more oftcn mycloid than 'lymphoid' features (Peterson *et al*, 1976; Catovsky *et al*, 1978) whilst in thosc cases prcsenting as Ph¹-positive acute leukaemia the reverse is the rule (Bloomfield *et al*, 1977). Many morphological. membrane and enzymic similarities between Ph¹-positive ALL and 'lymphoblastic' BC of CGL have now been found; similar features are seen in common-ALL (Ph¹-negative) (Janossy *et al*, 1978). In addition, early observations of a selective sensitivity to vincristine and prednisone in a proportion of BC cases (Canellos *et al*, 1971), particularly those of 'lymphoblastic' morphology (Cattan *et pl*, 1970; Marmont & Damasio, 1973). have now been confirmed in cases defined by their TdT content (Marks *et al*, 1978).

The question which arises is whether the presentation as ALL or CGL represents a diffcrent clinical manifestation of the same disease process, Ph¹-positive leukaemia, or, despite the overwhelming presence of the same marker chromosome. a distinction should be drawn between the two, because of their separate evolution and other differences, which will be discussed below.

Ph¹-Positive ALL

Numerous reports of ALL in which the Ph¹ chromosome was demonstrated have been published since the original description by Propp & Lizzi (1970). Only recently has it been realized chat this is not an uncommon phenomenon in adults presenting with ALL (Bloomfield *et al*, 1977) and-two series in which chromosome analysis was systematically investigated in adults with ALL suggest an incidence of 25% (Bloomfield *et al*, 1978 Catovsky *et al*, 1979). Secker Walker *et al* (1976) have observed an incidence of only 2% in childhood ALL and this may account for the absence of Ph¹-positive cases in the series of Oshimura *et al* (1977), although the latter observed one case since their study was completed. In patients presenting as acute myeloid leukaemia (AML) the incidence is of the order of 2–3% (Whang-Peng *et al*, 1970; First International Workshop, 1978b; Bloomficld *et al*, 1978).

A new and interesting feature of Ph¹-positive ALL cases is that if complete remission is

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achieved, some revert to a chronic phase CCL. Eleven such patients. mostly adults, have been described in the literature (Table I), the majority in the last 2 years. Two earlier par (Matrangelo *et al*, 1967; Canellos *et* of, 1972) have not been included because of *the* aut description as 'myeloblastic'. The Ph¹ chromosome was demonstrated on all the six occa when it was sought at diagnosis and evidence of 'lymphoid' features, other than morphol were also present (Table I). All patients responded promptly to therapy, vincristine prednisone in most, and the chronic phase was evident 2–36 months ktcr. This interval

TABLE I. Documented ALL cases developing chronic-phaw CGL (Ph¹+)

			ALL phase				
Aurhors	*Year*	*Age/Sex*	*Markers*	*Ph¹*	*Response to therapy*	*Time to develop CGL** (*months*)	*Overall survival* (*months*)
1 Tanzer *et al*	1975	28 F	nd	nd	CR	36	72†
2. Beard *et al*	1976	33 F	ALL (+)§	+	CR	12	12+
3. Gibbs *et al*	1977	54 M	ALL +)	+	CR	5	8+
4. Mauri *et al*	1977	37 M	nd	nd	CR	2	11
5. Mauri *et al*	1977	28 M	nd	nd	CR	6	16+
6. Fisher *et al*	1977	59 M	B an T (−)	+	CR	9	15
7. Formrn *et al*	1977	4 F	TdT +)	+	CR	24	60†
8. Harousseau *et al*	1977	50 M	nd	nd	CR	?	7
9. Catovsky *et al*	1978	18 M‡	ALL +)	nd	CR	6	29†
10. Oken *et al*	1978	20 M	TdT +)	+	CR	4	24
11. Crist *et al*	1978	11 M	TdT (+)	+	CR	a	15

nd = not done; CR = complete remission; ocher abbreviations as in text.

* All cases were Ph¹ (+) during rhc CGL phase.
† Myeloid blast crisis.
‡ Included in Beard *et al* (1976).
§ Positive with the anti-ALL serum.

depend on the type of maintenance therapy and whcthcr or not it is given continuously or intermittently; a high WBC with a differential typical of CGL may be more apparent in the latter. Our own data and that of others suggests that only 50% of 1'11'-positive ALL cases achieve a complctc remission. if remission is achicvcd. and if the paticnts do not revert to a chronic phase, the Ph¹ chromosome is oftcn no longer demonstrated in the bone marrow for variable periods of time (Forman *et al*, 1977; Gibbs *et al*, 1977; Mandel *et al*, 1977; Rausen *et al*, 1977; Janossy *et al*, 1978; Bloomfield *et al*, 1978). In one case (Gibbs *et al*, 1977) the bone marrow became Ph¹-negative during a 3-month period arid later reverted *to* a Ph¹-positive CGL (case 3, Table I). The others often relapse to a Ph¹-positive blast phase without evolving to the chronic-phase CCL.

A state of partial rcmission oftcn shows the coexistence of Ph¹-positive and Ph¹-negative clones (Propp & Lizzi, 1970; Beard *et al*, 1976; Gibbs *et al*, 1977). In thcrc cases, as well as our own, thcrc appears to bc a correlation bctwccn the prrccntsgc of bone marrow blasts and the percentage of Ph¹-positive metaphases.

The Ph¹ Chromosome

Two comparisons are possible between cases presenting as ALL (or AML) and as CGL: (i) whether the translocation t(9q+; 22q−) demonstrated in 92% of CGL cases (First International Workshop, 1978a) is equally frequent in Ph¹-positive ALL, and (ii) whether the percentage of Ph¹-positive metaphases corresponds to what is often seen in CGL.

Only three of the patients in Table I (cases 3, 7 and 9) had banding studies performed and in all t(9q+; 22q−) was demonstrated. In contrast, out of 18 patients presenting as ALL (and not reverting to CCL) only nine were t(9q+; 22q−) (Secker Walker & Hardy, 1976; Gibbs *et al*, 1977; Mandel *et al*, 1977; Oshimura *et al*, 1977; Janossy *et al*, 1978 Bloomfield *et al*, 1978; Gtovsky *et al*, 1979) and nine were 22q−, the exact site of the translocation not being identified (Forman *et al*, 1977; Bloomfield *et al*, 1378; Catovsky *et al*, 1979). The incidence of 22q− in a large series of CCL cases is less than 1% (First International Workshop, 1978a).

Detailed cytogenetic analyses have yet to be published to determine if all cases with 22q− have undetected variant translocations or if they just lack the long arm of chromosome 22 without evidence of translocation. All that can be said at present is that chromosome 9 appears to be normal in those patients. Whether this apparently major difference has any clinical significance will only become manifest when further patients with chromosome banding studies are reported.

90–100% of the metaphases were Ph¹-positive at diagnosis in the patients who develop chronic phase CGL (cases 2, 3 and 11, Table I) whilst in at least one-third of those who did not revert to CGL, not all metaphases were Ph¹-positive (Secker Walker & Hardy, 1976; Bloomfield *et al*, 1978). Abnormalities often associated with CCL in BC, such as a double Ph¹ chromosome, have also been observed in cases presenting as ALL (Harousseau *et al*, 1977; Janossy *et al*, 1978; Mauri *et al*, 1977; Bloomfield *et al*, 1978).

Clinical Evolution

Fig 1 illustrates the interrelationship between the various forms of presentation or of transformation of Ph¹-positive leukaemia. All the stages shown have been documented although they occur with different frequency. The data of this figure clearly suggests that an artificial distinction into the various stages cannot be made. Patients presenting as ALL or AML are well documented and, as shown in Table I, several patients have reverted to the chronic phase, including a patient presenting as AML (Worm & Pedersen-Bjergaard, 1977). This evolution has also been seen in patients presenting as CGL and later developing 'lymphoid' BC (Atkinson *et al*, 1975; Sébahoun *et al*, 1976). Termination as AML is not rare in patients presenting as CGL or developing CGL following an ALL phase (cases 1, 7 and 9, Table I; Sébahoun *et al*, 1976). Quite often, patients presenting as acute leukaemia achieve only a partial remission and, during this, Ph¹-positive cells (presumably blasts) and Ph¹-negative cells (presumably normal cells) coexist. A mixture of 'myeloid' and 'lymphoid' blasts has also been documented in several instances (Forman *et al*, 1977; Janossy *et al*, 1978).

Conclusion and Speculations

It is difficult to dissect what appears to be a multi-faceted disease (Fig 1) purely by an examination of clinico-haematological features. The strongest argument for this is provided

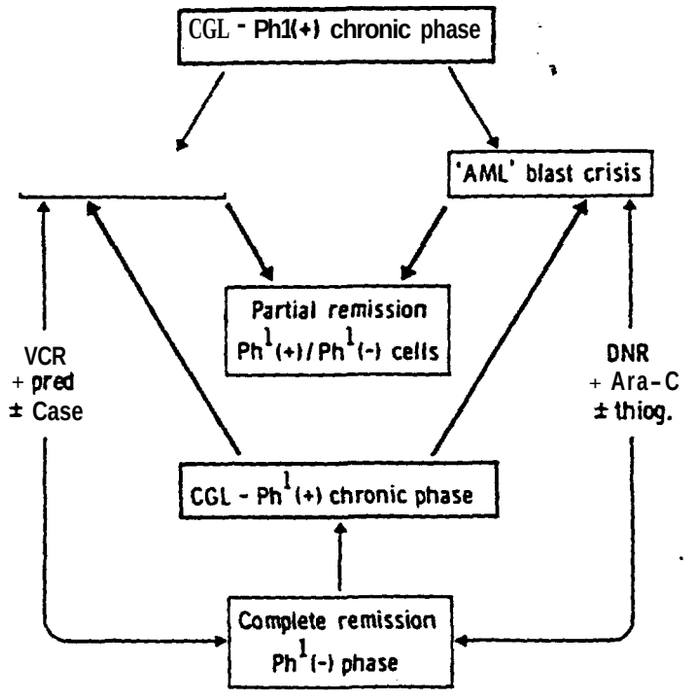


FIG 1 **Abbreviations: VCR, vincristine: pred. prednisone: L'ase. L-asparaginase; DNR .** daunorubicin; Ara-C, **cytosine arabinoside;thiog, thioguanine. For other** abbreviations see text.

for by the increasing number **of** patients presenting as ALL (rarely as AML) in whom transiti to CGL has **been** documented.

However, it is clinically important to consider separately Ph¹-positive ALL because of. high incidencein adult patients **(Bloomfield *et al*, *1977,1978;*** Catovsky ***et al*, *1979)*** and **becau** this disease appears to be associated with a lower remission rate and an overall worse prognos than Ph¹-negative ALL. Chromosome analysis is essential in the initial investigation of adu ALL and in atypical cases **of** childhood-ALL (Secker Walker ***et al*, *1976).***

Perhaps the **most** exciting point for furthcr study is the suggestion that the t(9q+; 22q− may bc significantly less common in paticnts presenting as ALL than in thosc presenting a CGL. Another important point is to understand the mechanism **of** the prcdominancc of Ph¹ positive metaphases in CGL not uniformly seen in the **ALL** phase, particularly during partia remission **(Fig1).**

Evidence accumulated **so** far confirms **the suggestion** that the Ph¹ chromosome may affect either a 'lymphoid' (presumably multipotent) stem ccll. or, more commonly. a myeloid **stem** ccll (Janossy *et al*, ***1976).*** The sensitivity to vincristine and prcdnisonc **of** the 'lymphoid' **stem** ccll may explain the relative **ease** with which a state **of Ph¹** negativity can **be** achieved. **The** elimination **by** therapy **of** a Ph¹-positive 'lymphoid' cione may **be** followed randomly **by** a Ph¹-positive (Icukacmic) or a Ph¹-negative (normal) stem ccll moving **into** the stem **cell** compartment in which haemopoietic differentiation and maturation occurs (the 'feeder' **stratum** of Killman, 1968). Which of these two events occurs will dcpcnd on **how many generations of stem cells arc** affected by the Ph' aberration and whether, indeed, **some** Ph¹-

negatives remain; this appears to be so in cases presenting as ALL. The chronic phase of CGL reflects the predominance of 'feeder' Ph^1-positive stem cell committed to myeloid differentiation. Because this clone provides functional haemopoietic cells, it inhibits or suppresses the existence of a normal clone and could expand slowly before it becomes clinically apparent. These features, plus the proliferative advantage provided by the chromosome marker, would make its elimination very difficult unless vigorous chemotherapy was used (Gee *et al*, 1978).

The Ph^1 chromosome and its disorders have once again opened up further fields for research into the nature of the chromosonic abnormality and of the mechanisms of stem-cell function in health and disease.

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