Changes in the Chromosome and Haemoglobin Patterns in a Patient with Erythro-leukaemia

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The relation between the constitutional hypoplastic anaemias and leukaemia is now well established (Garriga and Crosby, 1959), and a further point of similarity between the conditions is the relative frequency with which foetal haemoglobin synthesis has been observed in age-groups where the haemoglobin pattern would be expected to be of the adult variety (Beaven, Ellis, and White, 1960; Shahidi, Gerald, and Diamond, 1962). Although the chromosome pattern has been studied in detail in many forms of leukaemia, there is little available information about the changes in the constitutional hypoplastic anaemias of childhood (Sjölin and Wranne, 1962). Furthermore, there have been few chances to obtain consecutive information about the changes in haemoglobin and chromosome pattern during leukaemic transition.

This report describes the consecutive changes in the haematological, haemoglobin, and chromosome constitution of a girl in whom an acute erythro-leukaemic picture developed during the course of a long-standing hypoplastic anaemia.

Subjects and Methods

In order to compare the distribution of foetal haemoglobin in the child under discussion with that found in other acquired haematological disorders, blood samples were obtained from 71 persons with the conditions listed in Table I. Haematological studies followed standard techniques. Foetal haemoglobin was estimated using the method of Betke, Marti, and Schlicht (1959) and the intracellular distribution by the method of Kleihauer, Braun, and Betke (1957); using the photodensitometric modification of Sheppard, Weatherall, and Conley (1962). The electrophoretic, chromatographic, and fingerprinting techniques were as previously reported (Weatherall, 1963).

Five serial samples of peripheral blood and one of bone-marrow were taken from the child under discussion over a 12-month period for chromosome studies.

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The peripheral blood was cultured by a technique similar to that of Moorhead, Nowell, Mellman, Batipps, and Hungerford (1960) and bone-marrow was studied both without prior culture by the technique of Tjo and Whang (1962) and after a short culture period by the method of Ford, Jacobs, and Lajtha (1958). Spreading of cells was effected from 60% acetic acid by air-drying and subsequent staining either by lactic-acetoorcein (0-25%) or by Feulgen.

Case Report

P. B. was first seen in 1957, aged 8 years, at the Royal Liverpool Children's Hospital following a severe epistaxis. Her parents said that she had been small and pale as long as they could remember and that she was thought to be anaemic as an infant though she had not undergone haematological studies before 1957. No history of drug exposure could be obtained. Examination at this time revealed a very small, poorly developed child with pallor but no hepato-splenomegaly. A blood count revealed the following: Hb 7 g./100 ml.; WBC 3,000/c.mm. (polymorphs 42%, lymphocytes 43%, monocytes 9%, basophils 8%); platelets 24,000/c.mm. The red cells showed hypochromia and marked anisocytosis-poikilocytosis. The serum iron level was 300 µg./100 ml. The bone-marrow was hypocellular. She was treated with vitamin B12, folic acid, and blood transfusions, but she remained anaemic and thrombocytopenic, no improvement being noted on the addition of cortisone therapy. She underwent splenectomy in March 1957 whereupon the platelet count rose temporarily to normal and then slowly fell. By the end of May 1957, the haematological picture was similar to that when first seen with Hb of 8 g./100 ml. and 73,000 platelets/c.mm. She was maintained on prednisone and occasional blood transfusions from 1957 until July 1962. During this period the Hb fluctuated between 7-0 g./100 ml., the total white cell count between 3,000 and 5,000/c.mm. with a relative lymphocytosis, and the platelet count between 30,000 and 100,000/c.mm. The bone-marrow picture at this time remained only moderately cellular with an occasional bizarre nuclear pattern seen in the erythroid precursors.

She was first seen in Liverpool Royal Infirmary in
July 1962, at the age of 15, and was found to be small, gracile with no signs of secondary sexual development, and with a moderate lower dorsal kyphosis and marked pallor. Radiographs of chest, hands, skull, and long bones, and intravenous pyelograms revealed no abnormalities. Hb 7·5 g./100 ml., RBC $2 \times 10^6$/c.mm., PCV 22, MCV 94, MCHC 34%; platelets 110,000/c.mm.; WBC 2,000/c.mm. (polymorphs 35%, lymphocytes 58%, monocytes, 4%, basophils 1%). The peripheral blood smear revealed marked aniso-poikilocytosis with hypochromia, burr cells, and occasional nucleated red cells. The leucocyte alkaline phosphatase was normal. The bone-marrow was moderately cellular and showed erythroid hyperplasia; some of the red cell precursors were bi- and tri-nucleated and occasionally showed cytoplasmatic staining with the periodic acid-Schiff (P.A.S.) stain. The blood group was A, Rh negative. The serum iron was 320 µg./100 ml. and the serum iron-binding capacity 335 µg./100 ml. Serum vitamin B12 level was 200 µg./ml. Formiminoglutamic acid (Figlu) was not detected in the urine after an oral loading dose of histidine monohydrochloride. The direct and indirect Coombs tests were negative as was the Schumm's test. The serum bilirubin was 0·3 mg./100 ml., 24-hour faecal urobilinogen 125 mg. and urinary urobilinogen 2·7 mg. Paper chromatographic studies of the urine revealed a normal amino acid pattern, no abnormalities being noted on examination of the chromatograms under ultraviolet light. Column chromatography of several urine samples on a Dowex 1 chloride column using a hydrochloric acid gradient (0·001 M to 5·0 M) revealed no orotic acid peak, this being confirmed by Dr. H. J. Fallon, Yale University School of Medicine.

Treatment with vitamin B12, folic acid, iron, cobalt, pyridoxine, cytidylic acid, and uridylic acid produced no improvement in her haematological picture. She was maintained on prednisone 5 mg. three times daily from July 1962 until January 1963, the haematological picture remaining essentially unchanged.

Following a pneumonic infection in January 1963, the clinical and haematological picture showed a striking change (Fig. 1). Immediately before this change, the haematological findings were as follows: Hb 9 g./100 ml. Total nucleated cell count 2,000/c.mm. (polymorphs 16%, lymphocytes 58%, monocytes 2%, nucleated red cells 20%). In the subsequent month the total nucleated cell count rapidly rose to 19,000/c.mm. with the differential count showing polymorphs 0·5%, lymphocytes 5·5%, nucleated red cells 94% (17,850). During this period Hb remained between 5 and 7 g., despite several transfusions, the platelet count being between 20,000 and 40,000/c.mm. The bone-marrow at this time showed marked erythroid hyperplasia with many bizarre nuclear patterns. The patient was maintained on prednisone until September 1963, when she succumbed to a respiratory infection. During this time, the nucleated red cell count remained in between 8,000 and 15,000/c.mm., the cells showing a bizarre nuclear pattern with many bi- and tri-nucleated forms. During the final stage of the illness she remained very granulocytopenic and thrombocytopenic, a study of the buffy coat revealing an occasional immature cell of the myeloid series. No change in blood group constitution was noted during this period.

**Studies on the Haemoglobin Pattern.** Starch gel electrophoresis of the child's haemoglobin before January 1963 revealed haemoglobin A and A2 only, starch block estimation of the haemoglobin A2 fraction

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Platelets</th>
<th>W.B.C.</th>
<th>Foetal Hb%</th>
<th>Nucleated R.B.C.</th>
<th>Haemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>$10^3$/per c.mm.</td>
<td>$10^3$/per c.mm.</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIG. 2a. Preparation of P.B.'s blood prepared by the method of Kleihauer et al. (January, 1964) showing deeply stained foetal cells and adult 'ghost' cells. (× 890.)

FIG. 2b. Similar preparation from the blood of a patient with myeloid leukaemia and about 6% haemoglobin F. The acid resistant haemoglobin is quite heterogeneously distributed and there are few 'ghost' cells. (× 670.)
giving a value of 2.5%. Starch gel electrophoresis using a phosphate buffer system (pH 7.0) revealed no haemoglobin H, no inclusion bodies being seen on incubation of the red cells with brilliant cresyl blue. Foetal haemoglobin was not detected at this time by either the alkali denaturation or the acid elution techniques. After the rapid clinical deterioration in January 1963, with the appearance in the peripheral blood of many bizarre nucleated red cells, the level of alkali resistant haemoglobin rose to 5%. Using the acid elution technique, it was clear that the acid resistant haemoglobin was present in a single line of cells, the preparations containing about 5% of foetal cells, the remaining cells resembling normal adult 'ghost' cells with complete elution of the haemoglobin (Fig. 2). The presence of two distinct cell lines was confirmed by photodensitometric studies of photographic negatives of the acid elution preparations, the appearances remaining constant at a variety of elution pH values. These studies were repeated at intervals of two weeks over a period of six months. During this time the picture remained unchanged, the number of foetal cells showing an approximate agreement with the level of foetal haemoglobin.

The alkali resistant haemoglobin was found to be identical to genuine foetal haemoglobin by several criteria. Thus it showed an identical rate of electrophoretic migration on starch gel with pH 8.6, and on agar gel with pH 6.0. It had a similar rate of alkali denaturation and ultraviolet spectral properties as genuine foetal haemoglobin and behaved similarly to foetal haemoglobin on column chromatography using Amberlite, IRC 60. Large quantities of the foetal haemoglobin were prepared by column chromatography, concentrated in vacuo, and purified by repeated cycles of starch block electrophoresis. The fingerprints of tryptic digests of this purified material were compared with genuine foetal haemoglobin and found to be identical.

In vivo ferrokinetic studies and red cell survival studies using Fe59 and Cr51 labelling were initiated after January 1963. The Cr51 half-life of the red cells was 26 days and plasma clearance time of Fe59 was much reduced. Blood samples were drawn daily for 12 days and the percentage of iron incorporated was estimated, 25% of the initial dose being incorporated in 12 days. The foetal and adult haemoglobin fractions were then separated by chromatography and the percentage incorporation into each fraction was estimated. No significant difference in Fe59 incorporation into the two haemoglobin fractions was noted. Because of the child's poor physical condition and frequent transfusion requirements the incorporation of Fe59 in the haemoglobin F and A fractions was only followed for a 12-day period.

Family Studies. The parents of the patient and two sibs were healthy. Radiological studies of their hands were normal as were full haematological studies. In no case was the haemoglobin F level raised and the level of haemoglobin A2 was normal in each case.

### Foetal Haemoglobin Synthesis in Other Myeloproliferative Disorders and Aplastic Anaemias (Table I)

Increased amounts of haemoglobin F were only seen with any frequency in patients with acute 'blastic' leukaemia, multiple myeloma, acquired aplastic anaemia, and paroxysmal nocturnal haemoglobinuria. In each case the foetal haemoglobin was heterogeneously distributed throughout the red cell series, the appearances being similar to those found in the hereditary haemoglobinopathies and thalassaemia (Weatherall, 1964).

#### Table I: Foetal Haemoglobin Levels in Some Haematological and Neoplastic Disorders

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>No. Studied</th>
<th>No. With Increased Hb F</th>
<th>Range of Hb F Values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute blastic leukaemia</td>
<td>11</td>
<td>3</td>
<td>1.8-4.5</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia</td>
<td>6</td>
<td>1</td>
<td>6.5</td>
</tr>
<tr>
<td>Chronic lymphatic leukaemia</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Reticulosis and Hodgkin's disease</td>
<td>7</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>10</td>
<td>6*</td>
<td>2.4-4.7</td>
</tr>
<tr>
<td>Myeloid metaplasia</td>
<td>7</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Aplastic anaemia (acquired)</td>
<td>3</td>
<td>2</td>
<td>1.2 and 1.7</td>
</tr>
<tr>
<td>Paroxysmal nocturnal haemoglobinuria</td>
<td>2</td>
<td>2</td>
<td>4.0 and 6.9</td>
</tr>
</tbody>
</table>

*Note: Patients aged 15 to 75 years. In each case the Hb F was heterogeneously distributed.*

### Chromosome Studies.

The details of chromosome counts are presented in Table II. In all the blood samples except the last the cells counted gave a modal number of 2n = 46. Occasional cells had fewer chromosomes but these were attributed to preparation damage owing to random chromosome loss. A similar finding was made in the marrow sample except that an unusual proportion of polyplloid cells was also noted. This was greater in the direct marrow than in the culture but may be explained by differential growth. In the last sample of blood taken shortly before death, approximately 8% of cells (5 out of 62) were trisomic for a large chromosome, similar in size to a No. 6 (Fig. 3).

The outstanding feature of all the blood and marrow samples was the large number of cells showing chromosomes with very prominent secondary constriction zones (Fig. 4 and 5). Chromosome or chromatid breaks were also evident in some cells but these are considered to have arisen at the regions of the enhanced constrictions during slide preparation. The frequency of these secondary constriction zones (or breaks) is given in Table II, and from those cells fully analysed, the
TABLE II

<table>
<thead>
<tr>
<th>Date</th>
<th>Sample</th>
<th>No. of Cells with Counts of</th>
<th>Total No. Cells Counted</th>
<th>Total No. Cells Scanned</th>
<th>Polyploidy (%)</th>
<th>% Cells Counted showing Secondary Constrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/9/62</td>
<td>Blood</td>
<td>--- 42</td>
<td>42</td>
<td>---</td>
<td>---</td>
<td>17.0</td>
</tr>
<tr>
<td>2/4/63</td>
<td>Blood</td>
<td>41 41</td>
<td>41</td>
<td>---</td>
<td>---</td>
<td>19.5</td>
</tr>
<tr>
<td>2/4/63</td>
<td>Marrow (direct)</td>
<td>3 37</td>
<td>40</td>
<td>287</td>
<td>5.9</td>
<td>10.0</td>
</tr>
<tr>
<td>2/4/63</td>
<td>Marrow culture</td>
<td>3 30</td>
<td>30</td>
<td>199</td>
<td>3.5</td>
<td>Nil</td>
</tr>
<tr>
<td>2/4/63</td>
<td>Marrow culture</td>
<td>2 57</td>
<td>59</td>
<td>---</td>
<td>---</td>
<td>30.0</td>
</tr>
<tr>
<td>3/9/63</td>
<td>Blood</td>
<td>3 53 5</td>
<td>62</td>
<td>---</td>
<td>---</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Fig. 3. Chromosome preparation from a peripheral blood cell showing 47 chromosomes and analysed as trisomic for No. 6 chromosome. Note break in chromosome number 13. (× 1200.)

Fig. 4. Chromosome preparation from cell of direct marrow sample. Arrows indicate regions of enhanced secondary constrictions or breaks. (× 1200.)
Changes in the Chromosome and Haemoglobin Patterns in a Patient with Erythro-leukaemia

The chromosomal findings in this child are of interest. The significant increase in chromosomal fragility with many breaks and very prominent secondary constriction zones is not a regular factor of untreated leukaemia. Such a picture has been described in cells grown in a calcium-free medium (Sasaki and Makino, 1963), but there was no abnormality of calcium or phosphorous metabolism in this child. The positions of the constrictions and breaks seen do not always correspond with the sites of secondary constrictions in human chromosomes as reported by Sakelsa and Moorhead (1962), Ferguson-Smith, Ferguson-Smith, Ellis, and Dickson (1962), and Sasaki and Makino (1963). The lack of correspondence is most common in chromosome 1 where the constriction appears about midway along the lower arm, not near the centromere. It is in a similar position in chromosomes 7 and 9. In chromosome 2 the constriction appears mostly just below the centromere (Sasaki and Makino) but also occasionally in a more terminal position (Ferguson-Smith et al.). The constrictions in chromosomes 3 and 4 agree in position with those reported by Ferguson-Smith et al., and in chromosomes 2 and 3 the upper arms may also be affected (see Fig. 5).

The possible relationship of these chromosomal changes to the congenital hypoplastic anaemias has not yet been fully studied, but P. S. Gerald (1964, personal communication) has observed them in some but not all patients with Fanconi’s

## Discussion

The presence of 15,000–20,000 c.mm. of abnormal nucleated red cells in the peripheral blood, bizarre erythroid hyperplasia of the marrow, marked leucopenia and thrombocytopenia together with erythrokinetic evidence of a gross defect in haemoglobin synthesis are all findings regularly associated with the Di Guglielmo syndrome (Baldini, Fudenberg, Fukutake, and Dameshek, 1959; Sheets, Drevets, and Hamilton, 1963). The presence of a severe hypoplastic anaemia from an early age associated with the marked retardation of growth and scoliosis suggests that the neoplastic condition was superimposed on a congenital hypoplastic anaemia of the Fanconi variety. Although the outpouring of abnormal nucleated red cells into the peripheral blood only occurred six months before death, the marrow showed the presence of some bizarre erythroid precursors at least one year before.

<table>
<thead>
<tr>
<th>Chromosome No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4/5</th>
<th>6</th>
<th>7</th>
<th>9</th>
<th>13</th>
<th>15</th>
<th>16</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with breaks etc.</td>
<td>9</td>
<td>12</td>
<td>3</td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table III

**CHROMOSOMES WITH ENHANCED SECONDARY CONSTRICCTIONS OR BREAKS IDENTIFIED AFTER ANALYSIS**

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Fig. 5. Chromosome preparation of a peripheral blood cell (arrows as for Fig. 4). (× 1200).
anaemia. This requires further study, in particular the possibility of an abnormality of nucleic acid metabolism in congenital hypoplastic anaemia and the relationship of such chromosome changes to the subsequent development of leukaemic states.

The finding of a trisomy for a large chromosome, probably No. 6, during the transition to an erythro-leukaemic picture is of some interest. Such chromosomal changes have not been reported in the Di Guglielmo syndrome but occasional cases of acute leukaemia have been associated with a trisomy for a chromosome closely resembling No. 9 (Sandberg, Ishihara, Kikuchi, and Crosswhite, 1964).

The development of a 47-chromosome cell line in the blood after the picture of fresh erythro-leukaemia had developed is also of interest, because of the haemoglobin changes. Before the clinical deterioration and outpouring of nucleated red cells into the peripheral blood no foetal haemoglobin could be detected either by alkali denaturation or acid elution techniques. Coincident with the appearance of an erythro-leukaemic picture, the level of what appears to be foetal haemoglobin rose to 5%. This acid-resistant haemoglobin was present in one cell line. This is unlike the heterogeneous distribution of haemoglobin F found in myeloproliferative disorders with raised foetal haemoglobin levels (Zipursky, Neelands, Pollock, Chown, and Israels, 1962; Raper, 1963; and this study). It is also different from the heterogeneous distribution of acid-resistant haemoglobin observed in thalassaemia, the haemoglobinopathies, and congenital and acquired hypoplastic anaemias (Shahidi et al., 1962; Shepard et al., 1962). A single line of cells containing mainly haemoglobin F has, however, been demonstrated in a patient with erythro-leukaemia associated with an acquired D1-trisomy mosaicism (Ceppellini, 1963). In the children with the D1-trisomy syndrome who had increased levels of haemoglobin F (Huehns, Hecht, Keil, and Motulsky, 1964), it was heterogeneously distributed throughout the red cells (E. R. Huehns, 1964, personal communication). It is clear, therefore, that the foetal haemoglobin, found not uncommonly in the myeloproliferative diseases, is usually heterogeneously distributed, its occurrence in a single cell line being the exception. It is likely, therefore, that the mechanism of foetal haemoglobin production is different in the two types of intracellular distribution.

There is good evidence that the neonatal switch from foetal to adult haemoglobin synthesis (γ to β-chain) is determined at a specific genetic locus, and there is increasing evidence that, in addition to the structural genes controlling α, β, and γ-chain synthesis, there are also genetic mechanisms that control the rate of synthesis of these peptide chains (Conley, Weatherall, Richardson, Shepard, and Charache, 1963). To date, though there is increasing knowledge about the arrangement of the haemoglobin genes on their chromosome, nothing is known about the particular chromosome that carries these loci.

In the present case 8% of the cells were noted to be trisomic for a large chromosome, probably 6, at the same time as about 5% of foetal haemoglobin appeared in the peripheral blood, confined mainly to one cell line. Such a situation could have arisen in several ways. Thus if the γ-structural locus were found on this chromosome its triplication might result in the failure of the mechanisms that normally keep this locus repressed in adult life, with subsequent reactivation of γ-chain synthesis. Alternatively genes that form part of the regulatory mechanism for foetal haemoglobin synthesis might lie on the triplicated chromosome. It is also possible that the chromosome changes and haemoglobin findings are not directly related, the foetal haemoglobin synthesis following a somatic mutation in a neoplastic cell line. In the cases of myeloproliferative disorders, where there is increased foetal haemoglobin heterogeneously distributed in the cells, it is likely that the underlying mechanism is one of local alteration in environmental conditions in the marrow rather than a primary genetic event. A similar explanation has been invoked to explain the heterogeneous distribution of haemoglobin F in thalassaemia and the haemoglobinopathies (Shepard et al., 1962).

The findings of Huehns et al. (1964) and Ceppellini (1963) leave little doubt that a gene or group of genes present on the triplicated chromosome in the D1-trisomy syndrome are in some way concerned with γ-chain (haemoglobin F) synthesis and probably with the synthesis of the γ-chains of primitive embryonic haemoglobin. It is possible that one of the mechanisms mentioned above is responsible for this relation, but a further possibility has been recently suggested by S. H. Boyer (1964, personal communication) who has noted that haemoglobin A2 synthesis is delayed in infants with the D1-trisomy syndrome. Haemoglobin A2, the normal minor adult haemoglobin component, is, like haemoglobin A, present in low levels in the foetus, its rate of synthesis rapidly increasing in the neonatal period. If delayed haemoglobin A2 synthesis is confirmed in the D1-trisomy syndrome, it suggests that a locus may be present on the triplicated chromosome, which in some way is
Changes in the Chromosome and Haemoglobin Patterns in a Patient with Erythro-leukaemia


References

Concerned with maturation and that the changes in haemoglobins F and A, may be associated with this more general effect. The recent observation that, in infants with the D1-trisomy syndrome, there is a delay in the appearance of red cell carbo-nonic anhydrase, another protein that is only synthesized after the neonatal period, supports this possibility (Gerald, Walzer, and Diamond, 1964).

The study of the correlation between chromoso-mal changes and alterations in protein pattern is only in its infancy. The finding of increased levels of leucocyte alkaline phosphatase in mongolism with a 21 trisomy and a reduced level in chronic myeloid leukaemia in association with the Ph chromosome has suggested that the locus governing synthesis of this enzyme might be on chromosome No. 21 (King, Gillis, and Baikie, 1962; Nowell and Hungerford, 1964). This relation has become less clear, however, since it has been noted that, in patients with treated chronic myeloid leukaemia in complete remission, the leucocyte alkaline phosphatase returns to normal while the Ph1 chromosome persists (Frei, Tijo, Whang, and Carbone, 1964).

Summary

The haematological, haemoglobin, and chromo-some patterns have been studied in a patient with a constitutional hypoplastic anaemia during transi-on to an acute erythro-leukaemia. In the pre-leukaemia phase there were chromosomal changes characterized by frequent breaks and increased secondary constriction zones. No foetal haemo-globin was present. After leukaemia transition a line of foetal haemoglobin-containing cells ap-peared and a line of cells trisomic for a large chromosome, probably No. 6, was noted. The possible interrelationships of these observations are discussed.

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