possibly account for this result. In the light of a missing biological link for the putative association of the two conditions, the conclusion must clearly be that there is no increased risk for testicular germ cell tumours after vasectomy.

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Unusual Clonal Evolution During Blast Crisis of Chronic Myeloid Leukaemia (CML)

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THE PROGRESSION of chronic myelogenous leukaemia (CML) to blast crisis is generally associated with additional chromosomal abnormalities. The four most frequent changes observed are trisomy 8, isochromosome 17q, trisomy 19 and/or an additional Ph chromosome. In addition to these changes, more than 300 chromosomal abnormalities, involving so-called unusual or variant translocations, have been reported [1, 2]. We present a previously unreported chromosomal abnormality within a multiclonal marrow population in a patient with blast phase CML, where the clone containing the aberrant chromosome became the dominant clone.

The patient, a 49-year-old Caucasian male with a diagnosis of CML, was treated initially with γ-interferon (IFNγ, 9.8×10^6U) for 2 years without any significant response, and then recombinant interferon-α (rIFN α-2b, 6×10^6U) three times a week. He was maintained on rIFN α-2b, 6×10^6U. After 17 months of treatment, his disease entered complete clinical remission.

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Initial cytogenetic evaluation of our patient revealed the typical 46,XY,t(9;22)(q34;q11) karyotype of CML, and a positive *bcr* rearrangement. Two years later, although clinically in chronic phase, the dividing marrow cells began to display blast crisis abnormalities, with up to three additional clones, each clone containing one extra chromosome 17 and up to two extra chromosome 8s. Two years after detection of the additional clones, the patient was clinically in blast crisis. At that time, 88% of his dividing marrow cells contained a highly unusual aberration. A duplication of the long arm of chromosome 1 (q11→qter) had translocated to one chromosome 10(p12) with loss of the 10 (p12→pter) (Figure 1). A cell line with 48 chromosomes, including a +8 and +17 in addition to the der(10), became the dominant clone (49%). Five separate cell lines were present.

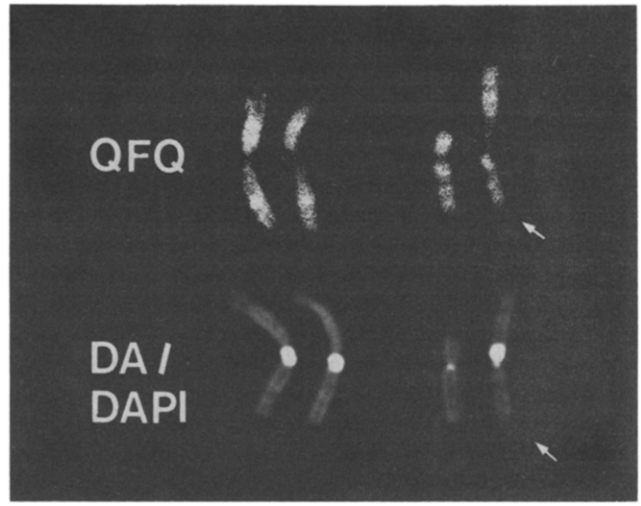

Figure 1. Aberrant chromosome exhibiting an unusual translocation involving chromosomes 1q and 10p. The centromere of chromosome 10 is retained in the translocation. QFQ, Q bands by fluorescence using G binding; DA/DAPI, binding technique.

A perplexing question surrounding the onset of blast crisis is whether additional cytogenetic aberrations initiate it or whether they are epiphenoma. In our case, the additional +8 and +17 chromosomal abnormalities proceeded the clinical onset of blast crisis. The presence of additional chromosomal abnormalities and, in a few cases, amplifications or mutations of protooncogenes in acute phase are suggestive of a possible role for additional genetic events in the evolution of CML. [3,4].

Recently, Ahuja and colleagues [5] demonstrated that transcripts of the p53 gene (a 53 kDa nuclear protein) were uniformly detected in chronic phase cells from 38 CML patients; however, in 10 out of 16 patients in blast crisis, p53 transcripts were either reduced or undetected. They also showed that heterogeneous anomalies in the structure and expression of the gene appear to be common for blast crisis but are generally not observed in other human malignancies. Numerous studies have suggested a role for the p53 gene located on chromosome 17p in cellular proliferation, regulation of the cell cycle and oncogenesis [6], and in several mouse erythroleukaemia cell lines, it appears to be acting as a negative regulator of cell growth [5]. It is of interest to note that the aberrant 48, XY,t(9;22), der (10),+8,+17 clone not only became the dominant clone, but further transformed by adding a duplicated 1 (q11→qter) translocated to the 10(p12).

The 1(q11→qter) abnormality has been observed in a transplanted CML patient [7], containing an unusual translocation t(1;3) (q11;p11) that underwent clonal selection involving six cell lines. The clone with the der(1) seemed to have gained a selective growth advantage and within 5 months of transplantation became the dominant line. The 1q11 break point has been reported previously in those cases of CML containing variant translocations [1, 2]. It appears that in at least those 2 cases of CML, the 1q11 breakpoint, in the presence of the altered *abl* oncogene, is conferring some type of advantage to those cells that are undergoing division, as both became the dominant clones within their respective populations. The mechanisms involved in the translocation may somehow be affecting the p53 gene, ultimately causing a reduction or blockage of transcription, thus providing a selective growth advantage to the aberrant clone.

It may be possible to further elucidate the mechanism(s) of clonal evolution in this biphasic disease through analysis of information from variant cases.

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5-HT_3 Receptor Antagonists in the Prophylaxis of Acute Vomiting Induced by Moderately Emetogenic Chemotherapy—a Randomised Study

J. Bonneterre and B. Hecquet

WE WERE interested in the study reported by Jantunen and colleagues comparing, in patients receiving a moderately emetogenic regimen, ondansetron, granisetron and tropisetron [1]. However, we would like to raise a number of points: although this is a cross-over study, no period and carry-over effects were looked for, thus preventing any definite conclusion. While period and carry-over analyses are not easy with three drugs, some papers have addressed such problems [2]. In Table 2 (unfortunately the number of patients in each group was not given), examination of the granisetron failure rates in each cycle shows that the differences are striking (2% at the first cycle, 13.6% at the second and 8.7% at the third), and could be explained by a period effect; the data on the patients evaluable for the three cycles are unfortunately not available. In Table 3, patients should only have been pooled in the absence of a period and carry-over effect.

Nausea was not evaluated in the study, although it is clear that moderate and severe nausea are very distressing side-effects for the patients. The type of chemotherapy was poorly defined—was the treatment always administered in one day? Finally, given the patient heterogeneity, a comparison of the clinical characteristics of the patients in each group should have been given (e.g. were there more chemotherapy naive patients in one group?). Unfortunately, the alcohol intake was not recorded.

An adequate statistical analysis of this study would be useful before any conclusion can be drawn.

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5-HT_3 Receptor Antagonists in the Prophylaxis of Acute Vomiting Induced by Moderately Emetogenic Chemotherapy—a Randomised Study

I. Jantunen and T. Muhonen

WE DO agree with Dr Aapro and Professor Bonneterre on the shortcomings of our study (alcohol intake was not recorded, nausea was not evaluated). It is also obvious that a cross-over design with three drugs includes many methodological problems. A parallel group design with 650 chemotherapy-naive patients would have been optimal for comparing these three drugs. Such a study cannot be accomplished without a large collaborative study group and financial support. In our study, the chemotherapy was administered in one day. During the first chemotherapy cycle, there were 17 chemotherapy-naive patients randomised to receive ondansetron, 15 tropisetron and 17 granisetron. The number of evaluable patients during each chemotherapy cycle has been added to the rewritten Table 2.

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