hypertrophic cardiomyopathy by DDD pacing. Third, despite the fact that the patients were mainly in New York Heart Association functional class IV before DDD pacing, in both types of cardiomyopathy a considerable increase in exercise capability is achieved.1,4 Moreover, in both conditions the beneficial effects of chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous

chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2 During 5 years' follow-up a continuous chronic DDD pacing continue to be evident when pacing is abruptly stopped.1,2

clonal deletions of mtDNA in the bone marrow (Pearson's syndrome) and the suppression of mitochondrial protein synthesis by chloramphenicol. Similar haematological defects occur in patients with MDS. This suggests a causal relation between the clinical features of this disorder and mtDNA in bone marrow. TGGE is a practical method to screen patients suspected of genetic mutation in defined regions of the mitochondrial genome.

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Mitochondrial DNA mutations in the myelodysplastic syndrome

SIR,—Rotig et al1 have reported the deletion of mitochondrial DNA (mtDNA) in the haematopoietic tissue of a patient with Pearson's syndrome, a fatal bone marrow disorder with clinical features similar to the myelodysplastic syndromes (MDS). This prompted us to examine patients with primary MDS for mtDNA mutations. The molecular analysis of mtDNA is usually difficult and requires complex methodologies such as DNA sequencing. Thermal-gradient-gel electrophoresis (TGGE)2,3 is a rapid alternative to screen for base mutations in specific regions of mtDNA.

We extracted high molecular weight DNA from a marrow aspirate taken from a 57-year-old white man at the time MDS was diagnosed (refractory anaemia FAB sub-type) and again 16 months later when he presented with acute myeloid leukaemia (AML). Standard sequence DNA was obtained from the peripheral blood of a normal white man and in-vitro polymerase chain reaction testing and comparison with CD4 lymphocyte counts: HIV infection 204(174) 213(131) 258(213) 145(183) 192(170)

Mean (SD) shown, tincluding 4 patients with stage II disease who went on to develop AIDS

In patients with stage II infection, β2-microglobulin dropped significantly at 3 months and 6 months (p < 0.05); at the same time CD4 counts rose significantly (p < 0.05). After 9 months of treatment β2-microglobulin stabilised. A similar drop in β2-microglobulin at 9 months (from 2.2 [0-6] to 2.7 [0-7] mg/l; p < 0.01) was seen in 4 of these patients who developed AIDS. CD4 counts in these 4 patients rose significantly up to 6 months, (from 61 [61] to 169 [164]); at 6 months; p < 0.01.

In the patients with AIDS serum β2-microglobulin fell significantly (p < 0.05) at 6 months, rising again at 9 months. CD4 counts were stable. 14 of the 36 patients died or had secondary opportunistic diseases. In these 14, β2-microglobulin dropped from 3.1 (1.0) to 2.8 (1.1) mg/l; at 9 months (p < 0.05) at 6 months, with stable CD4 counts.

These results show that serum β2-microglobulin concentrations fall in HIV-infected patients receiving zidovudine, as Lifson et al have reported. Increased serum p2-microglobulin concentrations are associated with mortality in AIDS patients.
to survival for HIV-infected patients, as found by Jacobson et al., could not be judged from \( \beta_2 \)-microglobulin values since there were no differences in concentrations between HIV-infected patients, who developed AIDS during the study, those who died, and those who presented with secondary opportunistic diseases.

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shown for single markers and for marker combinations. The -2 log likelihood estimate for the "Null model" (277.16) was improved in the "Full model" (238.45) with all six markers. NPT=neopterin, IFN=interferon, B2M=\( \beta_2 \)-microglobulin, CD4=CD4\%.

Bivariate analyses revealed a similar picture, showing neopterin, interferon concentrations were the best single predictors, followed by CD4 plus neopterin. Neopterin and CD4\% were the best univariate and bivariate models, respectively with and extends analyses of immune activation markers such as neopterin and CD4\%.

Predictive value for developing AIDS of immunological and virological markers measured three years after HIV-1 seroconversion.

For comparison of predictive values, -2 log likelihood estimates are shown for single markers and for marker combinations. The -2 log likelihood estimate for the "Null model" (277.16) was improved in the "Full model" (238.45) with all six markers. NPT=neopterin, IFN=interferon, B2M=\( \beta_2 \)-microglobulin, CD4=CD4\%, Ag=p24 antigen, Ab=anti-p24 antibody. Neopterin and CD4\% plus neopterin were the best univariate and bivariate models, respectively

interferon, and \( \beta_2 \)-microglobulin as significant joint predictors with CD4\%. Even more information was obtained by including the three best markers neopterin, interferon, and CD4\%. \( \beta_2 \)-microglobulin was strongly correlated with neopterin, and seemed to be a better predictor of AIDS later rather than earlier in the course of disease (eg, five years after seroconversion). In addition, the value of these markers may vary with the different manifestations of AIDS, since interferon strongly predicted opportunistic infections but not Kaposi's sarcoma.

Our results generally accord with the conclusions of Lifson and co-workers and contribute to the evidence that measurement of serum soluble immune activation markers improves the prediction of AIDS risk in individuals with HIV infection. Our data also support the view that immune activation is involved in the pathogenesis of AIDS.

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SIR,—Evaluation of 214 HIV-1 seropositive homosexual men by Dr Lifson and colleagues (June 13, p 1436) provides additional evidence that measurement of \( \beta_2 \)-microglobulin adds information to CD4 counts for estimating the risk of AIDS. This result accords with and extends analyses of immune activation markers such as \( \beta_2 \)-microglobulin and neopterin as predictors of AIDS.

We extended our investigation of a cohort of 131 homosexual men with incident HIV-1 infection to include various immunological and virological markers. In addition to CD4 counts, \( \beta_2 \)-microglobulin, and p24 antigen, we evaluated serum concentrations of interferon, neopterin, and p24 antibodies. On the basis of measurements at various year points—eg, three years after seroconversion—all markers apart from anti-p24 were significant predictors of AIDS risk in univariate analyses. Compared with the null Cox regression model, neopterin and interferon concentrations were the best single predictors, followed by \( \beta_2 \)-microglobulin concentrations and CD4 counts (figure). Bivariate analyses revealed a similar picture, showing neopterin, interferon, and \( \beta_2 \)-microglobulin as significant joint predictors with CD4\%.

SIR,—Serum concentrations of \( \beta_2 \)-microglobulin are used prognostically to monitor and predict progression of HIV infection and, as Dr Lifson and colleagues report, they have a good correlation with progression of the disease in homosexual and bisexual men. Other published studies have evaluated its use as a prognostic marker in that population, and in recipients of blood products. However, there is some evidence that drug-injecting behaviour can raise serum \( \beta_2 \)-microglobulin, and thus its prognostic reliability in HIV-infected injecting drug users (IDUs) may be affected.

We are conducting a prospective study to assess the prognostic value of serum \( \beta_2 \)-microglobulin concentrations and other surrogate markers in a cohort of 327 patients with HIV infection followed for a mean of 4.7 months. Serum \( \beta_2 \)-microglobulin concentrations were measured with a quantitative radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden) at 3–6-month intervals. Statistical analyses were done by means of the Statview II statistical package (Abacus Concepts, Berkeley, California, USA). 226 patients were drug users (69%), 52 were homosexual or bisexual men (16%), 45 were non-drug users, 19 were heterosexual men or women (14%), 3 were recipients of blood products (0–9%), and 1 (0.3%) had unknown risk factors for HIV infection. The table shows baseline serum \( \beta_2 \)-microglobulin concentrations according to risk factor and Center for Disease Control (CDC) staging. Serum \( \beta_2 \)-microglobulin concentrations did not differ between the groups with respect to risk factor for HIV infection, once CDC staging of the disease was taken into account. Reliable information about their drug-injecting behaviour could be assessed in 125 (55%) drug users. We classified drug users as non-injecting (non-IDU) when history, clinical signs, and urine toxicology analysis did not suggest injecting drug use for at least one month before baseline \( \beta_2 \)-microglobulin measurement. 97 of 125 drug users (78%) were non-IDUs, whereas 28 (22%) were IDUs. Mean serum \( \beta_2 \)-microglobulin concentrations at

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SIR,—We present a diagram (fig 1) of -2 log likelihood estimates for the full and null models for the \( \beta_2 \)-microglobulin concentrations and other surrogate markers in a cohort of 327 patients with HIV infection followed for a mean of 4.7 months. Serum \( \beta_2 \)-microglobulin concentrations were measured with a quantitative radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden) at 3–6-month intervals. Statistical analyses were done by means of the Statview II statistical package (Abacus Concepts, Berkeley, California, USA). 226 patients were drug users (69%), 52 were homosexual or bisexual men (16%), 45 were non-drug users, 19 were heterosexual men or women (14%), 3 were recipients of blood products (0–9%), and 1 (0.3%) had unknown risk factors for HIV infection. The table shows baseline serum \( \beta_2 \)-microglobulin concentrations according to risk factor and Center for Disease Control (CDC) staging. Serum \( \beta_2 \)-microglobulin concentrations did not differ between the groups with respect to risk factor for HIV infection, once CDC staging of the disease was taken into account. Reliable information about their drug-injecting behaviour could be assessed in 125 (55%) drug users. We classified drug users as non-injecting (non-IDU) when history, clinical signs, and urine toxicology analysis did not suggest injecting drug use for at least one month before baseline \( \beta_2 \)-microglobulin measurement. 97 of 125 drug users (78%) were non-IDUs, whereas 28 (22%) were IDUs. Mean serum \( \beta_2 \)-microglobulin concentrations at
TNFα in stool as marker of intestinal inflammation

Str,—Dr Braegger et al suggested that tumour necrosis factor alpha (TNFα) concentrations in stool provide a simple way to monitor disease activity in inflammatory bowel disease. They also measured TNFα in stools of 14 children with acute diarrhoea, of whom 3 had concentrations above the control range. They suggested that stool TNFα may be raised in infectious colitis. We have measured TNFα and interleukin-6 by ELISA in stool filtrates of children with acute diarrhoea.

Our study confirms that in children with shigellosis, TNFα concentrations are in the range reported for children with inflammatory bowel disease. We hypothesise that local production of cytokines and other mediators of the inflammatory response may mediate the local and generalised vasculitis that occurs in shigellosis. These data confirm the suggestion that stool TNFα is raised in infectious colitis. In other infective conditions, serum interleukin-6 is a better indicator of severity than TNFα. It would be of interest to determine whether the same relation existed in chronic inflammatory bowel disease.

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