An exercise test showed normal working capacity and no signs of coronary artery disease. Standard 12-lead ECG was still normal. Haemoglobin returned to normal within 2 weeks. After follow-up for 9 months, he has had no further signs or symptoms of heart failure.

This patient had an acute febrile illness followed by a rash, slight haemoglobin fall, and temporary heart failure. Recent parvovirus B19 infection was suspected and serologically confirmed. No other causes of heart failure, such as coronary artery disease or cardiomyopathy, were found. The anaemia was not thought to be important. We suggest that parvovirus B19 may be another cause of heart failure and should be looked for in similar cases.

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Increase in cancer incidence in younger birth cohorts

SIR,—Professor Adami and colleagues' conclusion (March 27, p 773) that cancer risks are increasing in younger birth cohorts in Sweden, is based on a misinterpretation of age-period-cohort models.[1,2] Age-period-cohort models cannot be used to attribute trends to either birth cohorts or period influences. The assumption that first and last period effects are equal to zero is made to reach a mathematical solution, and is arbitrary but vital to their argument. In the text and abstract of their reports cited by Adami, Clayton and Schifflers warn explicitly against the interpretation and presentation of regular trends as they are in Adami's fig 3. By altering the arbitrary central assumption, any regular cohort trend may be changed in a regular period trend, and vice versa. Adami's conclusions are therefore unsupported.

What remains is the signalled incidence increase during 1958–87. Although standardised incidence increased by 55% (men) and 30% (women) in these years, standardised mortality over the same period changed by +3·6% (men) and −10% (women).[3] If we accept Adami's argument that this change is entirely attributable to therapeutic improvements, an additional 49% of male and 44% of female cancer patients would have been cured during 1958–87. Most cancers are solid tumours of the breast and of the respiratory, gastrointestinal, and genitourinary tracts. Although progress has been made, there is no evidence whatsoever to support such a striking increase of therapeutic efficacy.

Earlier and more diagnoses are more likely to explain most of the improvements in prognosis. Adami himself showed a strong breast cancer survival increase in the 1970s, arguing that this trend corresponded with increased awareness of the advantages of early diagnosis.[4] No official screening policy was adopted, but this did not imply that all Swedish doctors disregarded the advice of the leading cancer societies or that Swedish people did not hear about the alleged advantages of early cancer detection. The argument that increased diagnostic efforts are not likely to produce the alleged cohort effects demonstrates again the risk of sophisticated statistical models more than anything else. As emphasised by Clayton and Schifflers, regular trends cannot be attributed to cohort or period effects.[2]

All cancer registers consistently show more favourable disease stages among younger birth cohorts, but at a price: earlier diagnosis means diagnosis at a younger age (lead time), of more slowly growing tumours which previously would have passed unnoticed (length time), and of early, hard to classify, lesions with an uncertain natural history (intestinal borderline polyps, bladder papilloma, early stage gastric and prostatic cancer, and so on). All will increase incidence, and bias estimates of underlying cancer risks. By applying sophisticated statistical models only to incidence or only to mortality, highly relevant information is neglected. We suggest that all available evidence should be examined to understand time trends: incidence, mortality, and prognosis.[5]

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SIR,—Professor Adami and colleagues' report shows the value of recording high-quality data over many years. The reported increases in the incidence of cancer in Sweden are large and generally consistent over the 30-year and the 80-year intervals, and Adami et al favour a direct link with changes in exposure to carcinogenic hazards. However, there is another hypothesis that would explain these increases.

Age-specific incidence is necessarily based on the chronological ages of individuals and it is assumed that chronological age parallels biological age. Other Swedish data suggest otherwise. Data for Swedish girls[1] show that age of menarche has fallen linearly from about 15·8 years in 1885 to about 13·0 years in 1968. In 1885 most girls with a chronological age of 14 years were prepubertal; in 1968 most girls aged 14 years were menstruating and were much more biologically mature. If we assume that menarche occurs at a set biological age, then the acceleration in biological age compared with chronological age is 0·0023 years per elapsed year per year of age for individuals. The rate of maturation has increased steadily in childhood and this pace, once set, probably continues throughout the lifespan.

Other evidence for increased rates of biological development, or biological ageing, comes from Swedish studies on the growth of children. Ljung and co-workers[2] have shown that the average prepubertal girl aged 10 years in 1968 was the same height as the average prepubertal girl aged 11·9 years in 1883. If height reflects biological age, then this change is an acceleration of biological ageing by 0·0020 years per elapsed year per year of age, which is very close to the rate calculated with age of menarche. For boys, the acceleration in biological age based on increased height growth was 0·0026 years per elapsed year per year of age.

This apparent acceleration in biological age compared with chronological age has been used to recalculate the expected age-specific incidence of cancer over the 30 years from 1958 to 1987. I have used the reported death rates from cancer for Sweden published by WHO.[3] Adami and co-workers have shown that these death rates differ from the incidence rates, but should approximate them. In the table, I have assumed that biological age equalled chronological age at the start of the 30 years, but that by the end of this period the biological age must exceed the chronological age. The expected incidences are calculated from biological ages.

The expected increase in the age-specific death rates from cancer due to the relative increase in biological age was 15% in young women, but close to 30% in older women. The expected age-specific increase in men aged 15–25 years was 6%, but in older men almost 50%. These predicted increases, based on increased biological ageing, are closely similar to those of Adami and co-workers for women, except in old age. The increases in men are higher than in Adami's fig 1, but the differences between men and

EXPECTED CHANGES IN AGE-SPECIFIC INCIDENCE OF CANCER DUE TO INCREASED BIOLOGICAL AGEING

Age group (mean chronological age)	1958 Mean biol age	1958 Recorded death rate (/100 000 per year)	1987 Mean biol age	1987 Expected death rate (/100 000 per year)	% increase in death rate
Women					
15–24 (20)	20	4·6	21·2	5·3	15
25–34 (30)	30	13·1	31·8	16·4	25
35–44 (40)	40	44·2	42·4	59·2	34
45–55 (50)	50	143	53·0	184	29
55–64 (60)	60	322	63·6	398	24
Men					
15–24 (20)	20	6·7	21·5	7·1	6
25–34 (30)	30	10·1	32·5	13·1	30
35–44 (40)	40	32·9	43·0	48·7	48
45–54 (50)	50	116	53·8	179	54
55–65 (60)	60	363	64·5	538	48

Biol = biological.
When mortality rate from cancer is calculated on basis of biological age, the increase in biological age associated with acceleration of maturation and growth produces increases in incidence of cancer at any chronological age.

women in this calculation are similar to the longer term increases shown in their fig 3.

There is another feature of the Adami data that supports the biological ageing hypothesis. They showed that men and women aged about 40 years in 1987 had almost no increase in the incidence of cancer. These people passed through their childhood in the years after World War II, when conditions were not easy for parents and children. If good environmental and social conditions lead to increased growth, health, and maturation, then these 40-year-old individuals may have been deprived as children and their lower incidence of cancer would result from the resulting slower growth and maturation. Data on their growth during childhood and their age at menarche would support or refute that idea.

I suggest that biological age does not necessarily parallel chronological age. Although it is usually impracticable, changes in disease incidence might be better based on biological rather than chronological age. Good conditions during childhood are associated with more rapid growth and earlier maturation. The associated increased rate of biological ageing may then lead to earlier malignant disease. If this hypothesis is correct, then we have the paradox that a good social and physical environment may lead to more cancer, whereas a bad environment protects.

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Authors' reply

SIR,—Although the use of age-period-cohort models needs considerable care and awareness of the limitation of the models, the situation is not as bleak as Dr Bonneux and colleagues indicate.[1-5] Indeed, such models are important in the analysis of incidence or mortality trends. In our original report we had full discussion of the methodological limitations inherent in these models, but a few additional comments seem warranted.

Age-period-cohort modelling can be divided into two steps. The first involves testing of various submodels against the full age-period-cohort model. This part of the analysis is fairly straightforward, since traditional statistical considerations usually allow the choice of the best model. In our data, we found that the age-cohort model was sufficient for women. For men, the full model was an improvement on both the age-period and the age-cohort model, but cohort seemed to be a more important factor than period.

The second step of the modelling consists of an estimation of the relative risks from the model identified in the first step. In our data, this scheme caused no difficulties for women, since we could use the age-cohort model, which has uniquely defined variables (although they could still be biased if there was a true period effect). For men the situation was more difficult, since the linear parts of a full model are not uniquely identified. As we noted in our report, all choices of further restrictions to force unique index estimates have drawbacks. Our choice of a linear period effect with slope zero was based on the arguments of Holford.[3-5] This assumption has the further advantage that it is almost equivalent to the method suggested by Clayton and Schifflers.[1,2] A possible result of this choice is that the cohort effect is somewhat exaggerated, because it may include part of the period effect. The only real alternative is to report no estimates at all, or to report several different sets of estimates, each based on specific assumptions. Such an approach needs to be considered when it is unclear which of the factors are more important, a situation we were able to avoid for men because of the clear importance of the cohort effects. Thus it is incorrect to deny the presence of the strong cohort effects in our data.

To what extent are incidence rates influenced by factors other than changes in carcinogenic exposure and disease occurrence? It is possible that screening, new diagnostic technologies, increased diagnostic intensity, drifts in histopathological criteria, and changing necropsy rates might result in earlier diagnosis or even overdiagnosis of cancer; these factors could perturb incidence trends, but only overdiagnosis can lead to sustained increases in incidence in the absence of an increase in true cancer incidence. Nevertheless, there is virtually no empirical evidence to support an important role for any of these possibilities. Hence, there is a substantial burden of proof for those who claim that they are quantitatively important.

All quantitative methods used to assess the burden of cancer have advantages and disadvantages.[6] Comparison of the incidence, and mortality and survival rates from the same setting are by definition mutually dependent. In fact, the decrease in case fatality estimated by Bonneux et al (and dismissed by them) agrees fairly well with our estimates for Sweden during the period 1960–84.[7] However, Bonneux and colleagues are incorrect in stating that we have claimed improved treatment accounts for the decreased cancer case fatality in Sweden. In fact, we have repeatedly stated that we believe other factors probably play the more important part.[6,7]

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Neonatal myoclonus and neuroblastoma

SIR,—Myoclonus occurs in various disorders in neonates,[1,2] but, to our knowledge, neonatal myoclonus has never been reported in association with neoplasms, in contrast to myoclonic encephalopathy of infancy.[3] We report a newborn baby with myoclonus who was found to have a neuroblastoma.

A 3740 g baby girl, who was born uneventfully at 39 weeks' gestation, developed myoclonic jerks in her sleep on the third day after birth. The cluster of jerks consisted of symmetrical rapid movements of the arms and/or legs that lasted for several minutes.