Commentary: Outliving the Risk for Cancer: Novel Hypothesis or Wishful Thinking?

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Early models examining the age distribution of cancer focused almost exclusively on mortality outcomes in populations ages 25 to 74 (Nordling 1953; Armitage and Doll 1954, 1957). These early studies integrated coherent observations from animal models with an understanding of epidemiological trends for specific cancer sites in order to generate testable models describing carcinogenic processes. Because diagnosis and reporting were considered to be unreliable at older ages, these papers limited their modeling to mortality data for adults under age 75. However, as early as 1969, Cook et al. noted that cancer incidence for some sites either rose more slowly at older ages or reached a peak and then declined (Cook et al. 1969). Moolgavkar, over several decades, has been developing biologically based, two-stage carcinogenesis models that incorporate cell kinetics, including tissue growth and differentiation rates (Moolgavkar and Knudson 1981), and has recently explored modifications that incorporate a decline at older ages (Moolgavkar et al. 1999). In other recent work, extensions that take into account not only cell mutation and kinetic rates, but also corrections for underreporting at older ages and population heterogeneity with regard to genetic susceptibility and environmental exposure, are predicated on achieving an age-specific maximum and a subsequent decline in cancer mortality (Herrero-Jimenez et al. 2000).

Pompei and Wilson (2001) have added another analysis to the literature examining the relationship between old age and cancer incidence using data from the United States, the Netherlands, and Hong Kong. They extend the theory beyond the point of declining incidence and propose that there is an age at which the population achieves a cancer incidence of 0. They conclude that "[contrary to conventional wisdom] if a person lives long enough, he or she may avoid cancer entirely". The authors assert that the age at peak incidence is invariant with respect
to cancer site and country, and further encourage readers to look for new biological theory to explain the existence of an incidence turnover and sharp decline, as the earlier versions of the multistage and clonal expansion models did not address it.

The authors make a number of important points, especially the need to focus on the fact that cancer incidence, as a population phenomenon, does not continue rising at the same rate in late age, but rather appears to flatten or even decrease in old age. Nonetheless, their arguments fail to be compelling for several reasons. (1) Their data do not support an invariant age at peak incidence, but rather one that is quite variable by cancer site. (2) The model fitting that results in a decline to zero incidence is based on data at ages well below this prediction, and the data they do have at high ages all show higher incidence than predicted, often statistically outside the predicted values. (3) They do not provide evidence against explanations such as low detection rates in the oldest, or for some sites, a reduction in the number of persons having the organ of interest, for observed data in those 85 and older. (4) They have no cogent arguments contradicting existing biological theories and corresponding models, which postulate that the flattening or decrease in cancer incidence at the oldest ages reflects a depletion of the pool of environmentally or genetically susceptible persons. Thus, the limitations to their arguments fall into three categories: those relating to the data and the fit of the model itself, those relating to data quality, and those related to the biological plausibility of their thesis and its consistency with other published research. We discuss each of these.

**MODEL DEVELOPMENT AND FIT**

The authors begin with data from the U.S. Surveillance Epidemiology and End Results (SEER) program for the years 1993 through 1997 for each gender for 17 separate non-sex specific sites, 6 separate sex-specific sites, all non-sex-specific cancers combined, and all cancers together. For each cancer site and gender, they model the incidence, modifying the Armitage-Doll power law by the factor $(1-\beta t)$ for $0 < t < \beta^{-1}$, where $\beta^{-1}$ represents the age when cancer incidence reaches zero. Finally, they evaluate the model fit to the SEER data, and then compare these fitted curves to data from three other sources. The authors seem undeterred by the fact that the maximum age group available for *developing* their model was 85 years and older (which, based on life-table analyses, they assigned to an average age of 90 years). Hence, for most cancers monitored by SEER, the incidence turnover is very close to the end of the observation period, and for many sites (bladder, leukemias, colon, stomach, pancreas), no actual turnover is even observed. Similarly, the authors are not bothered by the fact that the predicted ages at zero incidence, ranging from 93 to 112 in non-sex-specific sites (except for female melanomas), are, problematically, outside the range of observation (since all persons in the uppermost age category are assigned the value of 90). As for the evaluation of fit, it is quite poor for testicular cancer and Hodgkin’s disease, both of which peak before middle age.

The authors then compare these SEER-based models that extrapolate beyond the observed age range to three data sets, two of which contain more detailed information at older ages. In the Hong Kong data, similar to the SEER data, those 85 years and over are grouped into one category, and hence this analysis has the same limitations, *i.e.*, it provides no further information regarding incidence at the oldest
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ages. In the Dutch data, Pompei and Wilson plot age-specific incidence rates up to persons 95 and older and the corresponding 95% confidence intervals for nine site-gender categories, along with predicted curves from their SEER-based models. Interestingly, the lower 95% confidence bound for three of the nine data points for persons 95 years or older is higher than the predicted incidence, indicating that the beta-model produces far too steep a downturn, one that is not statistically consistent with the data. In the Dutch males, even when all other age groups have lower incidence than the predictions of the SEER model (e.g., colorectal, prostate, and bladder), those aged 95 or older have higher incidence than the model predictions. The authors note for the Dutch group, "Of interest, the oldest male lung cancer group has incidence almost zero at age 100" (Pompei and Wilson 2001). However, male lung cancer incidence at age 100 is still far higher than the maximum incidence experienced by Dutch females; moreover, none of the rates for the other sites even remotely approaches zero. U.S. mortality data also directly contradict the hypothesis, projected from the beta-model, that male lung cancer incidence reaches 0 at age 100: In 1990, the age-specific lung cancer death rate for U.S. males 100 years of age and older was about 200 per 100,000, essentially the same as the death rate in U.S. males 55 to 59 years old (Smith 1996).

The California data are the only other dataset examined by Pompei and Wilson (2001) for which the 85+ age group was further stratified. Not surprisingly, the predictions from the SEER-based model are closer, overall, to the California rates than to those from Hong Kong or the Netherlands (California contributes a good proportion of the SEER data). Nevertheless, the predictions of a decline to zero seem to be contradicted for the six site-gender categories. For lung cancer, the incidence rates for the three oldest age groups, 90 to 94, 95 to 99, and ≥100, are higher than the curve predicted by the beta-model in both males and females. In fact, the divergence between observed and predicted rates increases with increasing age, in spite of the fact that the observed age at peak incidence is actually younger than the SEER-based model predicts. Similar phenomena seem to be operating for the other sites in the California population.

The discrepancies between the fitted beta-models and the actual data from the Netherlands and California are significant, in that these are the only data with stratification above the age of 85. These data provide no support for the hypothesis of a decline to zero incidence at around 100 years of age. It therefore appears that the excellent fit statistics for the beta-models reported by Pompei and Wilson may be largely due to first, the close fit throughout the period of the rising incidence, and second, the use of data that has a single category for all those aged 85 or over. It is well known that the fewer the number of data points, the better the fit.

A second major limitation in the work of Pompei and Wilson (2001) is the lack of support for their conclusion that the age at peak incidence is invariant ("There is apparent remarkable uniformity of the age at peak incidence across all adult cancers." "The tabulations of age at peak incidence ...are quite uniform." "this constancy of t*" "the same average value"). Despite their assertions to the contrary, the ranges of predicted peak ages across SEER-reported sites, excluding the gender-specific ones, are 56 to 92 years for males, 51 to 95 years for females. Even if one also excludes the two lowest values for each gender, the range is 79 to 92 years for males and 78 to 95 years for females. Note, however, that the actual observed range of ages
at peak incidence (as opposed to the model predictions) has a wider spread, since those sites with younger peaks begin to decline earlier than the model would predict (e.g., male larynx observed peak is 73 years, predicted is 79 years, female thyroid observed peak is 47.5 years, predicted is 64 years), and there are insufficient data to determine the actual peak when it occurs within the oldest age category. The authors go on to say that the standard deviation for this distribution is 3.7 in males, which would yield a distribution in which 67% of the peaks were in a range of 7 years, with a further 33% outside that range. In females, they report a standard deviation of 7.1, which would indicate 33% of peak incident ages are outside a range of 14 years. These data hardly support the statement that 35 adult cancers "peak at close to the same age."

Their plots (Pompeii and Wilson 2001) also contradict the idea that age at peak incidence is invariant across populations. Dutch prostate cancer peaks at about 90, while in the SEER population, it peaks at age 73. In California, the lung cancer peak occurs earlier than in SEER data in both males and females. Instead of glossing over these differences in search of some universal truth, one could ask, for instance, how the antismoking campaign in California may have altered the incidence rates over the life course. Similarly, the ages at maximum incidence for female breast and colon cancers in Hong Kong are quite different from predicted, reflecting the importance of lifestyle and culture on the incidence of these cancers.

Equally disturbing is their distortion of previous authors' work on this question. Pompeii and Wilson cite Cook et al. (1969) as having found that "the data did not support variation in the age at peak incidence." In fact, Cook and colleagues made no reference to age at peak incidence in this regard, but rather reported that the degree of curvature was not associated with incidence level.

**DATA QUALITY**

The data regarding quality of diagnostic data at very old ages does support underascertainment. Pompeii and Wilson cite the Dutch study as showing that about 15% of cancers in those 95 years and older have not been histologically confirmed. Yet this difference is quite plausibly just the tip of the iceberg, since it does not even address non-diagnosis of cancers. Undetected cancer in the elderly may be even greater. For instance, it is likely that physicians do not aggressively conduct cancer screening among persons with Alzheimer's and other senile conditions or other conditions in which quality of life is severely compromised. As morbidity of this type increases with age, it could result in missed diagnoses of cancer. Other phenomena contributing to greater differentials in diagnostic completeness by age are the barriers to health care among the elderly, particularly the elderly poor.

A few examples illustrate this point. Prostate cancer incidence varies dramatically by the use of the PSA (prostate specific antigen) test; use of the PSA is also lower in older men, and some investigators even suggest the benefits of screening in men over 70 is outweighed by the physical and psychological costs (Potosky et al. 1995). In women, the presence of a uterus or ovaries is a precondition to being at risk for cancer in those organs, yet women who have undergone hysterectomy or bilateral oophorectomy remain in the denominator of the SEER rates. An analysis of U.S. national survey data from 1976 to 1980 indicated that cross-sectionally, among 18 to
74-year-old women, more than 1/3 had undergone at least one of these surgical procedures (Symanski and Hertz-Picciotto 1995). Thus, medical practices, either through screening or surgical procedures, can create artifactual distortions of the apparent incidence rates for cancer. While these distortions are unlikely to lead to zero incidence at any age, they are substantial and probably contribute to the decline in some cancer sites.

**BIOLOGICAL PLAUSIBILITY**

Cancer is not a single disease, but rather many separate disease processes. It is, therefore, not surprising that a turnover might be observed for some cancers and not others. In their earliest multistage model, Armitage and Doll observed the logarithmic increase in cancer mortality with age in cancers of the stomach, esophagus, colon and pancreas, sites for which there had not been a recent historical change in mortality. They specifically excluded cancers of the lung and bladder because “a proportion of the cases of cancer of the lung is believed to be related to cigarette smoking which has become more prevalent in the last 50 years and a proportion of the cases of cancer of the bladder is due to occupational hazards, to which men have been exposed for various periods at various ages. On the hypothesis that carcinogenesis is a multi-stage process, therefore, cancer at these sites would not be expected to show a uniform relationship between death rates and any power of age.”

They also excluded “hormonally related cancers” (breast, corpus uteri, ovary, cervix uteri, prostate) because they believed hormone level and therefore cancer risk would be heterogeneous with age.

Many other authors have since published models that attempt to explain the turnover with age in terms of a depletion of a population of susceptibles, who have both genetic susceptibility and environmental exposure (Cook et al. 1969; Herrero-Jimenez et al. 2000; Finkel 1995). Unfortunately, although Pompei and Wilson discuss this work, they do a poor job explaining why they dismiss the theory. First, they argue that heterogeneous susceptibility is not plausible, asserting that the distribution of susceptibles would have to be quite similar across cancer sites to produce peaks at close to the same age when absolute incidence varies 100-fold. However, age at peak cancer incidence actually varies fairly widely, as described above, and therefore, by their own arguments, so could the distribution of susceptibility.

Second, they claim that the model used by Finkel (1995) requires 100% susceptibility for the turnover to occur. They provide no evidence for this assertion, and the analysis by Cook and colleagues (1969) indicates the exact opposite: only when the pool of susceptibles is considerably below 100% does the age incidence cease to increase monotonically, under the Armitage-Doll model. Their third argument rests on an experimental study of genetically inbred mice showing turnover in cancer incidence at 80% of the lifespan. The relevance of this observation is questionable. Did all animals in this study develop cancer simultaneously? If not, then even genetically homogeneous animals provide evidence of heterogeneous susceptibility, which cannot, from such a study, be distinguished from stochastic variation.

Considering the data displayed by Pompei and Wilson (2001) for all of the various cancer sites for different nations together, it appears that for some sites, such
as the lung, larynx, breast, thyroid and brain, true declines in incidence are observed at the oldest ages; for other sites such as pancreas, esophagus, melanomas, multiple myelomas, and urinary bladder, a flattening, but not a decline, is observed at the oldest ages. Finally, there are some sites, such as stomach and colorectal cancers, that show declines in some populations and not others. It is only the predicted age at 0 incidence that is fairly uniform—but this is a hypothetical projection for which there is little data, and what there is provides direct evidence to the contrary.

The pool of susceptibles at any age is a function of the age distribution for other causes of death that share common risk factors with the cancer(s) of interest. The range of lifestyle factors that have been identified as causing cancer are limited—cigarette smoking, diet, exercise, occupation, and infections are each associated with many different sites (Harras et al. 1996). These factors are influential in mortality from cardiovascular disease, which accounts for 1/3 to 1/2 of all deaths. Moreover, the different social and environmental experiences that people have before, during, and after the years that they participate in the workforce may account for some commonality in the timing of exposures to very different social, dietary, and environmental risk factors. Finally, cohort effects due to lifestyle, medical and other societal changes are likely to influence numerous cancer sites and alter the age distribution of cancer incidence. Cook et al. (1969) demonstrated how downward pointing curves based on cross-sectional data can be produced by changes over time/age in prevalence of carcinogenic agents. For these reasons, the birth cohort approach of Herrero-Jimenez et al. (2000) is likely to be the most informative in teasing apart age effects from birth cohort effects. Without such an approach, age effects could be confounded by cohort effects.

Cook et al. rejected the idea of a limited pool of susceptibles but favored the hypothesis of changing environmental factors (1969). Notably, however, their rejection of the former explanation for a downturn was based on the hypothesis of genetic susceptibility operating alone, and did not encompass an interaction between environment and genetic susceptibility. Current thinking suggests that virtually all cancers are a function of such an interaction (Finkel 1995; Khoury et al. 2000). Thus, the conclusion of Cook and his co-workers that changes in the prevalence of exposure could account for downward or upward curvature in plots of the log incidence against age may also be consistent with a role for heterogeneous genetic susceptibility.

Pompei and Wilson do a service in drawing attention to the cancer incidence at old age. As they note, the observation that cancer incidence flattens at old age is not new, but the idea that cancer incidence may reach zero appears to be novel. They contend that the failure of the Armitage-Doll power law to predict incidence at old age is likely to reflect a problem with cellular theories. However, most other authors (including those who introduced the earliest models), by noting the importance of cohort effects, accepted the difficulty of evaluating cellular mechanisms using population data (Armitage and Doll 1954, 1957; Cook et al. 1969). Pompei and Wilson fail to do this. In a 1985 review of multistage models of carcinogenesis, Armitage (1985) comments that, “In many areas of biomathematics the ingenuity of the mathematician often seems to run ahead of the ability of the biological scientist to provide the data needed to validate the mathematical models.” Despite their
ingenuity, Pompei and Wilson have not come up with data validating their models nor have they provided reasons to reject a perfectly valid hypothesis regarding variation in susceptibility.

REFERENCES
Response to “Outliving the Risk for Cancer: Novel Hypothesis or Wishful Thinking?”

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We thank Professors Hertz-Picciotto and Sonnenfeld for their carefully considered comments, and for the opportunity to clarify our results and interpretation. We follow the same organization of their comments, in our response.

MODEL DEVELOPMENT AND FIT

As emphasized by the commenters, the SEER data for bladder, leukemias, colon, stomach, and pancreas cancers do not show actual incidence turnover for the age range reported. However, in each of those sites where data from other data sets exist for older ages (Dutch and California data for bladder, colon, stomach), the incidence turnover is present, and the peak is very close to the Beta model predicted age. It is worth noting that for the above 5 cancer sites not achieving turnover in the age range reported by SEER, the Beta model explains 1.00/1.00, 0.99/0.99, 1.00/1.00, 1.00/1.00, 1.00 of the male/female data variance (according to the Cox criterion) for those 5 SEER cancers, respectively. The near perfect model fit values, along with the fact that three of the five were subsequently proven to show turnover very near the predicted age, gives us some degree of confidence that the other two will also show a peak near the predicted age when data become available.

As for testicular and Hodgkin’s disease, we consider those cancers to be outside the range of our Armitage-Doll cancer creation modeling assumption, since they appear to be from quite different age-dependent mechanisms than the other 30 or so cancers. We conducted the model fit for completeness of data reporting. These cancers do, however share a common characteristic of incidence trending down at the oldest ages reported, and thus, we believe, are subject to the same biological mechanism (whatever it may be) causing the turnover for all of the other cancers.

Regarding the fits to the Dutch and California data for ages beyond that reported by SEER, the Beta model would not be expected to fit as precisely as it does the data for which the fit was actually derived. We consider the Beta model to be an adequate first approximation in its predictions at ages >90, since it is able to correctly predict the turnover location, and considering the simplicity of the model, it does remarkably well in predicting the approximate downward slope. Since the SEER data are the most complete below age 85, we chose to use extrapolations to the best fits to
SEER to compare to the turnover in the other data sets. Our comment regarding the Dutch lung cancer incidence reaching almost zero at age 100 is in comparison to its peak value at age 80.

Our claim that the age at peak incidence is remarkably uniform between sites must be considered in relation to alternative models, which all appear to predict the age to change as the incidence changes. At our reported standard deviation of 3.7 and 7.1 years for males and females, respectively, this is approximately ±4 to 8% variation of the age at peak incidence, compared to a factor of two change predicted by previous models, all of them appearing to be based on one variation or another of the “running out of candidates” approach (mathematically, the pdf must approach zero as the cdf approaches one for whatever group or subgroup is considered).

Cook et al. described their results in terms of curvature as opposed to age at peak incidence, but it is different words for the same mathematical result. Their model is a modified Armitage-Doll power law, which they derived as $\ln I = a + k \ln(t) - \ln[C + (1-C) e^{F/C}]$, where $F = e^{t/(k+1)}(k+1)$ to include a susceptibility fraction $C$. This expression produces a factor of two variation in age at peak incidence with factor of 100 variation in susceptibles fraction — a similar result as the unmodified A-D power law. They did not find the degree of curvature (and hence the location of the peak) to change with incidence as suggested by their model, and thus Cook et al. themselves rejected the susceptibles hypothesis.

DATA QUALITY

We cannot prove the reliability of the incidence data at the oldest ages. We simply accept them at face value while alerting the reader to their importance, providing relevant evidence where we can, and suggesting that science only advances by believing data and seeing where they might lead. Importantly, we cite the small, but growing body of direct pathology evidence that cancer prevalence flattens or reduces at the oldest ages, which appears consistent with incidence reducing at those ages, and not consistent with incidence increasing at the oldest ages. Although the commenters question the validity of the turnover data, they also point out that many authors have published models attempting to explain this turnover with a susceptibles depletion hypothesis. We accept this as support for our position, since those many authors explicitly share our tentative acceptance of the turnover data.

BIOLOGICAL PLAUSIBILITY

We concur with the commenters that cancer is a complex group of diseases, but nonetheless if there are undiscovered biological principles applicable to all of them, it is worth our effort to attempt to find those principles (and the effort of commenters to challenge them). Variation in susceptibility is one candidate for the turnover, which the commenters propose as a perfectly valid hypothesis. Unfortunately, it does not appear that this hypothesis had settled the matter of the turnover in incidence.

Amongst the reasons we looked beyond the susceptibles hypothesis were opinions on our results expressed to us by two of the foremost investigators in this field,
Sir Richard Doll and Suresh Moolgavkar. Both were troubled by the notion of groups who are immune to cancer, noting that cancer probability must approach certainty if: (a) the dose is sufficiently high (Doll 2001); or (b) time is sufficiently long (Moolgavkar 2001). Further, while the various models might all be “fixed” by making the number of nonsusceptibles vary appropriately with site, this appeared to us to be a somewhat arbitrary “ad hoc” explanation.

The Cook et al. study is in many ways similar to ours, in their attempt to identify general principles for cancer creation to include the oldest ages, by examining the age distribution of 31 types of cancers in 11 populations and applying a modified version of the Armitage-Doll model. They conclude: “No evidence was found to suggest that the shape of the observed relationship could be attributed to attenuation of a limited pool of susceptibles.” As noted by the commenters, they proceed by suggesting variation in carcinogen exposure as a possible cause, but avoid the inclusion of this hypothesis as part of a “susceptibles” mechanism. Although not stated by them, including exposure in the susceptibles hypothesis suggests that if a person is not exposed to the carcinogen, they are immune to the cancer. In the end, Cook et al. essentially concede the limitations of mathematical models to shed light on the underlying biology, a concession we propose might be premature.

As an example for discussing the commenters’ concerns about Finkel’s model, if 25% of the population were immune, there would be a turnover when the cumulative incidence begins to approach 75%, as occurs with the Cook model. Finkel’s model does not appear to have any persons completely nonsusceptible, and therefore, one might expect it to be necessary to approach 100% cumulative incidence before turnover must necessarily occur. We are not aware of any analyses of the Finkel model that shows actual downturn in incidence when cumulative incidence is less than one, but we cannot completely rule it out on purely mathematical grounds.

We consider the mice data to be quite important in weighing the evidence for and against susceptibility. Quoting the commenters, many other authors have published models proposing depletion of a pool of susceptibles based on those who have “both genetic susceptibility and environmental exposure.” The mice were bred and housed to have as little variation as possible in either, yet show statistically significant turnover in incidence at about 80% of lifespan. Indeed as the commenters suggest, the mice did develop cancer at different times in their lifespans, which leaves only stochastic variation. This stochasticity assumption is inherent in any Armitage-Doll or Moolgavkar type of causality model.

In the time since our paper was accepted, we have concentrated on studying the growing field of cell replicative senescence, a possible mechanism we suggest briefly in our paper. It appears that this may be a good candidate for the biological phenomenon we were searching for, since it seems widely accepted that: (1) cellular replicative capacity is limited, a fact known for 40 years; (2) it has been observed in vitro and in vivo for many cell types, both animal and human; (3) it is closely related to the ageing process; (4) it is a dominant phenotype when fused with immortal tumor-derived cells; (5) it is considered to be an important anti-tumor mechanism, since a senescent cell cannot produce cancer; (6) cells senesce by fraction of population, rather than all at the same time; and (7) senescent cells continue to function...
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normally, but are unable to repair or renew themselves. (Wynford-Thomas 1999; Faragher and Kipling 1998; Campisi 1997, 2001; Reddel 2000)

As outlined in our paper, senescence leads to the Beta function if the cumulative probability of finding a given cell is not senesced reduces linearly as age increases, to a value near zero at the oldest ages. This is mathematically the same as finding the population fraction of non-senesced proliferating cells reduces to near zero at the oldest ages. The literature suggests just such properties: a) percent of non-senesced cells decreases linearly with number of cell divisions to near zero (Hart and Setlow 1976; Thomas et al. 1997; Wynford-Thomas 1999); and b) replicative capacity of human cells in culture reduces approximately linearly as a function of donor age (Yang et al. 2001; Ruiz-Torres 1999).

Senescence appears to have all of the necessary properties to fit the data, and to be a biological endpoint of sufficient certainty and overwhelming effect to stop the carcinogenesis process. To the best of our knowledge no other modeler has yet included senescence in an attempt to explain the incidence turnover. Work is proceeding to explore this hypothesis, which we intend to present in a new paper. Since epidemiologic data at old ages is inevitably sparse and less reliable than data at younger ages, we believe that the solution or solutions to understanding of these data will only come from combining epidemiology with animal and in vitro data.

Again our sincerest appreciation to Professors Hertz-Picciotto and Sonnenfeld for their thoughtful discussion.

REFERENCES

Campisi J. 2001. From cells to organisms: can we learn about aging from cells in culture? Exp Gerontol 36(4-6):607-18