Oncogenes—no to reductionism?

SIR — Your *News and Views* annotation on "Oncogenes, reductionism and all that" (*Nature* 3 February, p.369) to my mind obscures an anterior debate. Holism and reductionism are modes of thought, the recognition of which is useful so that their more extreme manifestations can be subject to criticism, which, incidentally, seems to consist of gibes in *Naturese*. Most scientific endeavours have little consciousness of operating in either fashion but, to an outside observer, follow a course between the extremes. At times pressures from outside the academic community, "Rothschild" for example, can temporarily distort the pattern by asserting that there is some purpose in scientific endeavour and here, to my mind, lies the nub of the matter.

Working in an institute of cancer research one is sensitive to the criticism (not gibes, note!) that from the point of view of cost-effectiveness little seems to have been accomplished. One's colleagues on the other hand often argue that of course we need to know more before any good effect can derive from the large cost. Whether we should learn more by application of holistic or reductionistic method is not usually debated in those terms but the balance which is struck between clinically orientated and fundamental research is the outcome arrived at by drift rather than design. Thus, to my mind, the proper argument is not whether the scintillating new discoveries of the molecular biologists, manifestations of reductionism if you like, are futile, but whether science has a purpose. If it does we should almost certainly set about it in a different way.

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SIR — The *News and Views* article "Oncogenes, reductionism and all that" (*Nature* 3 February, p.369) is a little unfair to the reputable biologist (discredited vitalist or not) who would receive the welcome news of the recent contribution molecular biologists have made to the cancer problem with reserved scepticism. Cancer research is in an exciting phase, where there are now the means to understand cancer in its proper biological context for the first time. The ultimate aim of cancer research, which I would define as removing the intellectual humiliation and relative clinical impotence which afflicts clever people faced with a common disease, is already proceeding by generalization towards the elimination of that definition of cancer which sets the disease apart from all others, and in some way apart from the biology of living organisms as a whole.

Cancer can be defined as an abnormal relationship between the cellular contents of a malignant tumour and the host in which it originates, such that the normal processes of growth control and differentiation do not occur either because of a primary cellular defect within a component of the neoplasm or because of an intrinsic or acquired abnormality of the host. There is no known universal constitutional defect of a cell which can, without reference to the host, be considered *a priori* to confer the properties of neoplastic growth. The normal function of oncogenes is not known, hence the impact of the oncogene in biological terms cannot be fully assessed.

It is amazing that one probably minor and insignificant biological role of the oncogene (that of causing cancer) is developed into the state where the naïve reductionist might believe that it was inserted into the genome by a jocular deity to cause the specific disease for which more than modest research funding is readily available. The importance of these findings, in relation to cancer, cannot be ignored, but neither can the work on differentiation, genetics, immunology and epidemiology. The theorist (or the author of the *Nature* article) who believes that in the light of present knowledge it is possible to objectively debate the "first cause" argument in support of the oncogene in cancer hypothesis is misinformed.

The real advance lies in the fact that we may shortly achieve enough knowledge of the cancer state to set out the ground rules for such an objective debate. As an unashamed and (I hope) reputable biologist, why need I be castigated for holding the view that currently the oncogene hypothesis is naïvely reductionist?

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Thalassaemia

SIR — Orkin *et al.* in *Nature* of 23/30 December 1982[1] elegantly demonstrated that decreased synthesis of mutant globin β^E chains is due to abnormal processing of the β-specific mRNA primary transcript. This explains the previous finding of decreased mature mRNA in Hb E reticulocytes[2]. Thus, a qualitative change in globin structure in associated with a quantitative change in its production. This is a vindication of the "structure-rate" hypothesis proposed by Itano a quarter of a century ago[3] and further elaborated by Ingram and Stretton[4]. At that time it was suggested that an electrophoretically silent or a synonymous codon replacement might be present in β-globin in β-thalassaemia. If this entailed the requirement for a tRNA species absent or scarce in erythroid cells, it would explain why the polypeptide chain was synthesized at a reduced rate[5].

Apart from the special case of Hb Lepore, the search for a structural abnormality in the β-globin chain in β^+ - thalassaemia has since failed. However, we now have a clear example of a β-globin chain which was already known to be structurally abnormal, and in which a reduced rate of synthesis (β^+ - thalassaemia) is indeed a direct result of the structural abnormality. It turns out that the link between structure and rate is not at the stage of translation, but rather at the earlier stage of processing of the primary transcript.

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Dürer's technique

SIR — Nobody who could recognize a truncated rhombohedron when he saw one would have doubted that this is the polyhedron shown in Albrecht Dürer's drawing "Melencolia" (1514) and recently discussed in *News and Views* by Philip Ritterbush[1]. The only questions relate to its proportions. Assuming a threefold axis of symmetry the proportions of the solid object before projection could have been recovered by stereogrammetric techniques, as described by H.C. Longuet-Higgins[2]. However, the whole drawing (and others by Dürer) has been analysed by E. Schröder, as to the techniques used for the projection, in the light of Dürer's own manual of geometry, "*Underweysund der messung. . .*" (1525)[3].

Schröder shows that in Dürer's rhombohedron, projected in the special orientation with its threefold axis vertical, the diagonals of the faces of the untruncated rhombohedron are closely in the ratio $\sqrt{3}$ to 2. Thus, the rhombohedral angle α is 82° to an accuracy which excludes the possibilities of the golden section, which would need $\alpha = 72°$ and the nearest rhombohedron of calcite ($\alpha = 76.1°$). The c/a ratio is thus 3/2. Moreover, the overall height of the object is equal to the horizontal diagonal of the faces.

Thus, it seems that the polyhedron is simply an exercise in accurate draughtsmanship and that the art historians have made rather heavy weather of its explanation. The integral proportions show that no particular mineral was intended, although Grigoriev and Shafranovskii[4,5] had concluded that the polyhedron was an octahedron of fluorite ($\alpha = 60°$) but that the figure represented had $\alpha = 72°$.

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