Some reflections on the NOTE/DoReMi workshop on 14 June 2010.

I attended the NOTE workshop as part of my role in the FP7 ARCH project (http://arch.iarc.fr/), specifically to help me assess the role NTE might play in the health detriment that could have been accrued from the exposure to Chernobyl fallout in Europe. Basically I was looking for guidance from NOTE on the mechanisms underlying NTE. Both ARCH and NOTE finish later this year so the issue is urgent.

The morning session reminded me of walking through a street market with the vendors volubly advocating their wares. The rate at which experimental results were fired at the audience was, for me at least, overwhelming and it was impossible to accommodate them into a coherent mechanistic "story".

However, I detected in the room something that would not be found in a European street market, namely the proverbial elephant, the name of which nobody present dares to utter. That "elephant's" name in this case is "epigenetics" a word which was, I think, articulated only once in the morning session. If NTE's are effects that do not depend on molecular damage to DNA that is relevant to the endpoint being measured they are not "genetic" and therefore are "epigenetic", meaning either not "genetic" or "over and above genetics".

In the afternoon the "establishment" testified to their faith in the existing radiobiological paradigm as a basis for risk estimation and application in radiological protection while regretting the inevitable inherent uncertainty accruing from having a "big hole" on the mechanistic front and acknowledging that this might eventually (but not soon?) be filled by an understanding of NTEs. I can have sympathy for their plight because what was presented in the morning did little to fill that hole. Maybe that was not the intention.

These "defenders of the faith" may find consolation in the current plight of evolutionary biologists. At the end of last year the results of a 20 year long microbiological experiment (*1*) where an evolutionarily challenged (lactose reduced nutrient) bacterium was grown over 20,000 generations and the mutations accrued and the relative fitness (adaptation) of the bacteria measured at intervals. The experimenters are now faced with the uncomfortable fact that this unique experiment does not support the dogma that genetic change underlies evolutionary adaptation; if there is no genetic explanation for evolutionary adaptation it also must be an epigenetic phenomenon. No doubt there will be many praying for the eleven replicates of this experiment (still to be analysed) to demonstrate that this first result is aberrant: I would put money on the prayers being in vain.

The importance of correct and agreed terminology was touched upon several times during the morning and the term "epigenetic" is a danger zone in this respect. The term, as originally defined above, has been high jacked to mean regulation of transcription by marking of DNA and chromatin and this leads to confusion if the need is to discuss epigenetic effects in a generic sense. I suggest we should stick to the linguistically derivable meaning "over and above genetics" and place "chromatin marking" as a sub-category.

Much as I believe that epigenetic processes dominate the effects of radiation, especially at low doses, I can't help being captivated by the prospect floated by Dudley Goodhead, namely, that we should have a paradigm that did not violate Newton's Laws of Motion. As these Laws are time independent the idea that we should find a paradigm that allows half of us (or all of us half the time) to grow younger by the year is close to irresistible. The impediment I see to this is that it is easier to get the theory to fit the facts than the facts to fit the theory (except in politics). The fact is, introducing irreversible dynamics into physics theory has been a major challenge.

DoReMi, which occupied the last section of the meeting, is still young and perhaps expectations of it should not be too high, but I have yet to detect a burning desire to get to grips with where the

science should go in order to shed light on the so far insoluble low dose problem, something we were promised in Stuttgart last year. Terms have been thrown around like “a systems approach”, “an integrative approach”, “a molecular epidemiological approach” etc., which as far as I can see have advanced little beyond hand-waving over the past year. (I would of course like to be proved wrong.) As Dudley also advocated “systems biology” as a way ahead and I think I know what this might mean I would just note that a recent publication offers cold comfort.

M pneumonia is a parasitic bacterium that as evolved from more complex bacteria to have a minimal genome of only 689 coding genes. It is, therefore ideal for a genome wide systems approach in terms of its metabolism. Accordingly, a complete metabolic map has been constructed (*2*). By manipulating the nutrient conditions in some 3,000 kinetic experiments the researchers show that the metabolic map predicts the outcomes in terms of metabolic rates etc.. However, what they found puzzling was that *M pneumonia* is able to perform tricks characteristic of more complex bacteria for which it does not have the appropriate transcription factors (*3*). The authors speculate that some form of regulation at the post translational level is active, indicating not only epigenetic effects but a serious failure of the systems approach deployed.

The term “systems” is another terminological minefield. The German scientist, Ludwig von Bertalanffy developed General System Theory (*4*) in the 1940s and it had become part of the syllabus in science departments and medical schools in German universities by the 1960s (Christian please note). von Bertalanffy was careful to discriminate between systems that were open to information and closed thermodynamically and those that were open in both senses. Living systems fell in the latter category and thermostats in the former. Kitano, in the early 2000s (*5*), led a campaign to resuscitate systems approaches under the heading “computational systems biology” and it is the Kitano approach that Yus et al (*2*) took in their treatment of *M pneumonia*. In 2007 Kitano (*6*) states “*Ultimately, the theory* [computational systems biology] *will have to be interfaced with thermodynamics.”* Well said! So Yus et al it seems have proved that *M pneumonia* is more than a thermostat.

If the cell is a complex dynamic system, and Feinendegen thinks it is (*7*), then there is some way to go before we have a computational approach to systems biology. There are, however, alternative approaches and they need to be explored.

DoReMi has to address the reality indicated by the strands of evidence accruing in domains outside radiobiology and those do indeed point to dealing with the cell as a complex and irreversible dynamical system (and therefore not a Newtonian dynamical system or closed thermodynamic system) regulated through the direct interaction of the products of the DNA coding and the phenomenon of self-organisation.

Finally back to NOTE. The stated objective of the project is to find a new paradigm. I have detected some confusion over what would constitute such a new paradigm. Thomas Kuhn explores this subject in depth (*8*). NTEs serve, in this case, as the anomaly that cannot be explained under the prevailing paradigm and the need for a resolution of the anomaly to satisfy the needs of radiological protection, the crisis. Anomaly and crisis are the precursors to revolution and a new paradigm in Kuhn’s view. Discovering the identity of the “messengers” that mediate the bystander effect or finalising a definitive list of endpoints characterising genomic instability would not constitute new paradigms. The discovery of x-rays by Roentgen is informative. What first attracted Roentgen was the glow from a barium platinocyanide screen when the cathode ray tube was switched on. He was not the first to observe this as several such tubes were in use. Only when he had demonstrated the unique properties of the rays, that they travelled in straight lines and cast shadows, etc., could his revelation be described as a discovery and out of that discovery was born the new paradigm of ionising radiation, leading to new theories and practicalities, for example, the need to shield cathode ray tubes. The new paradigm was the combined experimental observation and the basis for assimilating the discovery into the scientific thought process, which blossomed into radiation physics, chemistry and biology. Roentgen’s work gave life to a new genre of science.

NOTE's challenge to find a new radiobiological paradigm is somewhat different. Radiobiology is a sub-discipline of biology and biology is (or should be) underpinned by physics and this raises the question of whether the new paradigm is confined to radiobiology or has wider impact: one imagines it must be the latter.

That point aside, experience (*8*) shows that when the new paradigm emerges only a few will recognise it as such and many will respond with disbelief and even hostility, maybe until their dying day, as did Joseph Priestley in respect of Antione Lavoisier's interpretation of his experiment that yielded, in his words, "dephlosgisticated air", or as Lavoisier is credited as having conjectured, oxygen (*albeit* thinking it was something else). The famous Austrian physicist, Ludwig Boltzmann, who proposed the relationship between entropy and the frequency of macroscopic states in a gas kinetic system, is alleged to have committed suicide because of the hostility from fellow scientists in Vienna to this now foundation stone of physical chemistry.

I therefore detect a fatal paradox here in terms of how the success of NOTE will be judged. If history is anything to go by, if NOTE is successful in finding a new paradigm most of the cognoscenti will regard it as a failure, unable to recognise the value of the new paradigm, while if NOTE fails to find a new paradigm those same people will regard it as a success, confirming in effect their faith in the existing paradigm: It appears then that NOTE's success lies in its failure, or *vice-versa*!

Keith Baverstock
Rapporteur
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