The History of Radiobiology and the Contributions of L. H. Gray

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Support for radiobiology has a long history at the Rockefeller Foundation (RF). One of the precursors of the RF's natural sciences division, which funded scientific research, was the International Education Board (IEB). It supported scientific scholars in many different nations to further world cooperation. The IEB wished to identify, or create and maintain, centres of excellence and to encourage training of young researchers in them. Many countries supplied both the centres and the young researchers. The maintenance of excellence was exemplified in two statements by the IEB's director, Wickliffe Rose. The board's aid would "help the strong," and its policies could "make the peaks higher". The IEB was a very early supporter of radiobiology and funded research in the 1920s on X-ray derived mutations of *Drosophila*, effects of ultra violet radiation on tissue development and work by Egor Lorenz in 1926, after he embarked on radiobiology studies.[1] Similarly in 1932, Raymond E. Zirkle was supported for alpha particle radiobiological work and later at Berkeley, University of California, for irradiation work at the then unique and recently completed cyclotron.[2] When the IEB was dissolved in 1929 and its functions assumed by the

RF, the IEB's flexibility was retained. Both the RF's natural sciences and medical divisions collaborated in supporting certain projects, without turf wars or other rivalry and both divisions would often collaborate to encourage and support funding for cross disciplinary research.

An overwhelming emphasis on multi-disciplinary approaches to the natural sciences, which the RF chose to support, was adopted soon after Warren Weaver became this division's director in 1932. He wrote, "I was convinced that the great wave of the future in science, a wave not yet gathering its strength, was to occur in the biological sciences."[3] This opinion was supported by the RF's Trustees who, in the spring of 1933, "voted to make experimental biology the field of primary interest in the natural sciences."[4] Such enthusiasm for a multi-disciplinary approach is particularly suited to radiobiology, which studies how radiation interacts with living material of all orders of complexity, from cellular components to cells, to tissues and finally to complete organisms. Hence elements of physics, chemistry, biochemistry and biology must all be applied. Niels Bohr shared this opinion of the RF, that a future application of physical and chemical sciences should be the elucidation of biological problems. Although he was a leading physicist, he encouraged biology research in his own laboratory and in close collaboration with August Krogh and George de Hevesy, a former chemist who discovered new artificially radioactive nuclei and first described and used the radioactive tracer method. He applied it to very many biological and medical processes - some mentioned below.

The RF decided no longer to fund 'pure' physics and chemistry, but rather to support applications of these fields as a means of elucidating mechanisms and problems in biology. Warren Weaver expressed this succinctly by saying that to advance biology one had "to concentrate on biology, but not on biologists"[5] and overall he had a very great influence on the RF's espousal of radiobiology.

The RF supported many of the important inter-war figures in science[6] including: 1) Hevesy (supported by the RF for 25 years, both personally and through his collaboration with Bohr and Krogh, who were funded by the RF from 1934 for their cross disciplinary work, long before that term was in common use); 2) Ernest Lawrence (whose cyclotron greatly increased the range of available radionuclides and radiations and who encouraged particle radiotherapy); 3) Theodor Svedberg and 4) Max Perutz. These persons in particular aided development and application of radiation, for they used or developed this modality, so advancing the progress of radiobiology. All of them were Nobelists, some obtaining their prizes well after they first received RF support.

The RF's apparently wise foresight in recognising that an important future application of physics and chemistry would be the solving of biological problems is totally obvious now, with today's available hindsight. This is crystal clear after even a most cursory study of the major biological advances of the last few decades. Such farsightedness on the part of the RF is well known and has been clearly described in various books and publications. But the specific and particular relevance of this philosophy to ensuring progress in radiobiology, which is a young and especially multidisciplinary science, has not previously been noted, to my knowledge. Already in the early 1950s the RF was supporting a wide variety of radiobiological and radioactive marker studies, including tumour uptake of certain marked molecules, the photosynthesis mechanism, pyrole pigment metabolism and vaccine structure. This tracer technique, first used by Hevesy, was greatly extended and widely applied by him as a result of the continuing support of the RF (also refers to footnote 6).

Of particular note is the RF's prescient support, as early as 1953, for the diagnostic use of positron emitters.[7] Only in the present century has this application become commonplace. The RF also supported activity which indirectly promoted radiobiological research. For example, it assisted the International Commission for Radiation Protection

which arranged an international conference on radiobiology in 1958, although there was very little presented there which described basic mechanisms.[8] However, the RF recognised this and in the same year offered support to Zenon M. Bacq to perform such research.[9]

Not only was basic study of different radiation modalities encouraged by the RF, but also investigation of radiation levels on biological processes, as early as 1937 for work by Frederic Joliot-Curie in Paris and by others in Utrecht.[10] Further crucial contributions of the RF to radiobiological understanding include its genetic effects. Relevant research by Herman Muller and his colleagues at Indiana University was funded by the RF starting in 1945.[11] Because of the RF's support, which continued for over a decade, these researchers became pre-eminent in their fields in the USA and in the world. Research support for others resulted in the discovery that infant mortality was doubled for children born to consanguineous marriages between irradiated persons, compared with non consanguineous marriages between the irradiated.[12] All this resulted from an early (1947) formal policy statement that the RF would support "studies of molecular structure of substances of biological interest, so-called **radiobiology** *[my emphasis]*, including the use of isotopes."[13]

Not content with supporting all these successful and eminent researchers, the RF was also an early proponent of radiobiology teaching, supporting programmes at the University of Pittsburgh, Duke University and Florida State University in the later 1950s.[14]

In the USA the Atomic Energy Commission (AEC), US Atomic Bomb Casualty Commission (USABCC) and National Research Council (NRC) were also important participants in radiobiological activity. It is most fortunate for the present study that the Rockefeller Archive Center's (RAC's) papers of J.C. Bugher and D.W. Bronk include many relevant records of these three bodies. In radiobiological terms the AEC was principally concerned with fall-out from atmospheric atomic weapon testing, radiation protection (of the general public and those who worked with radioactive materials), etc. After World War II

(WW II) there was the introduction of nuclear reactors and nuclear medicine procedures and consequently much research into radioprotection (closely related to radiobiology). The USABCC was solely concerned with the after effects (genetic and other) of the atomic weapons used in Japan. All these activities are most extensively documented and have an occasional direct relevance to my studies. The details of this relevance will have to be identified and teased out after completion of more detailed study. Even so, it must be noted that the greater part of this material is of limited relevance to my search. The U.S. National Research Council's (NRC's) support for radiobiology was principally funded by the RF so, at the RAC, there are detailed accounts of how these funds were disbursed. However, there was little support for basic research into radiobiological mechanisms. Most of the NRC's interest was directed towards more practical matters, such as allowable exposures to radiation, use of radionuclides for diagnosis and therapy, radiation units of absorbed dose, etc.

For many, the first considerations of radiobiology arose after the use of atomic bombs in WW II. But the RF and IEB had been involved in scientific aspects of the subject long before WW II, as noted above. In 1945, when contemplating the relevant science, the RF also considered its social and moral aspects. These included the prevention of war and aid towards a world community by "keeping currently familiar with the whole developing program of UNO in order to report to us the appropriate possibilities for the RF to consider."[15] Also, the importance of paying special attention to Russia at that time was recognised and so the RF aided Columbia University to establish an advanced centre of Russian studies and teaching. During WW II, the RF took note of the US government's requirement for secrecy and for this reason, in supporting radiobiology associated with war-related nuclear research at the University of Chicago in 1943, described it as "research in industrial medicine".

After the war, the RF participated in obtaining a Presidential agreement to set up the USABCC, whose functions have been described above. At this time the RF did not neglect its concern for humanitarian application of practical applications of its radiobiology expertise. In 1950 the RF arranged for the supply of medical radionuclides to nations requiring them, but which then had no means of production, in particular Austria.[16] In this and other ways the statement in the RF's charter, "to serve human welfare throughout the world" was executed through applications of ionizing radiation. The RF demonstrated a moral (and pragmatic) stance on all matters associated with radiobiology (and of course in other fields too). It is of note that in 1959 D.W. Bronk, President of the Rockefeller University and Trustee of the RF, spoke out at a Senate Appropriations Committee hearing. He protested against NRC researchers needing security clearance even if they worked in totally unclassified fields. The USAEC finally agreed to remove this limitation on researchers not concerned with classified information.[17]

The RF's policies were principally concerned with increasing knowledge. To this end basic radiobiology studies were encouraged, even though for many years the AEC and other US government funding in this field (e.g. through the National Academy of Sciences [NAS]) were principally concerned with its deleterious effects on humans, protection against ionizing radiation, maximum permissible exposures, absorbed dose units (definitions and standardisation, etc). Yet the RF additionally promoted basic studies in mechanisms of radiobiological action. Even so, a senior officer of the RF wrote in the early 1950s that, "various forms of radiation have similar effects on all living things." This displays ignorance of the important differences in such effects, which depend independently on the type of tissue and radiation modality. However, soon after this statement, appropriate knowledge was clearly gained by the RF's officers. Aware of the public's widespread ignorance of radiobiological matters in the face of passionate interest resulting from atomic weapons, the

RF expended much effort in disseminating information about ionizing radiation at many technological levels of society and aided the establishment of an Atomic Information Committee in 1945-6. Also in 1946, the RF supported an extensive investigation into sociological and other similar aspects of the field to increase knowledge of public and other understanding, and it funded the organisation of a conference for very senior members of companies producing electronic items (also refers to footnote 15).

Gerard R. Pomerat was a RF investigating officer especially concerned with radiobiology and associated matters. He was a man with considerable insight and knowledge. Particularly valuable are his descriptions of the setting of various scientific investigations in the wider range of research. An example of this is his monitoring and support of clinical experimental radiotherapy at the University of Cambridge.[18] Knowledge obtained by him and others was digested by the RF's Programmes and Policy making body and aided establishment of its activity relevant to radiobiology after 1946. For those with medical interests (and many others, who may have an interest in cancer), the main initial, and abiding reason for an interest in radiobiology is its relevance to the use of ionizing radiation in radiotherapy, still a most important method for treatment of cancers and other neoplasms. However, ionizing radiation itself can cause cancers and other less serious side effects, therefore radiobiological investigations can allow optimisation of all these characteristics of cancer management. Because of this, the RF was aware of the use of particle accelerators for radiotherapy at a very early stage. This was principally through Pomerat, who was well acquainted with the early Californian use of neutron radiotherapeutic beams in the late 1930s.[19] The subsequent essential study (for patient safety and optimal treatment effectiveness) of the relevant basic radiobiological mechanisms was therefore understood and supported by the RF. This is a good example of how a broad interest in a subject may permit early recognition of methods with a great potential. Even so, about five decades elapsed

before particle radiotherapy began to become generally available. To accelerate the necessary theoretical understanding of radiobiological mechanisms Pomerat and some of his colleagues at the RF searched out the basic studies of Louis Harold Gray and others (starting in 1949) and worked to allow the RF to support it. For example, esteemed advisors of the RF (Alexander Hollaender, ORNL and John Lawrence, University of California at Berkeley) were respectively quoted by Pomerat as saying, "Dr. Gray is perhaps the best man in the world to give the physical interpretation of biological effects of radiation"[20] and his laboratory is "the finest place in England for radiation physics on the animal experimental side".[21] The RF acted on these opinions by funding long term visitors (especially RF fellows) to work with Gray and also invited him to request support from the RF.

I obtained much useful information during my study period at the RAC in April 2009, concerning the history of radiobiology. The philosophy of the natural sciences division of the RF, adopted in the early 1930s to support natural sciences as a means of elucidating biological problems, fortuitously encouraged a great interest in radiobiology, an archetypically multidisciplinary field of study which is grounded in physics, chemistry, biochemistry, classical biology, etc. Many of the initial radiobiological studies were applied and only later was there a significant shift towards studies of the basic mechanisms. The RF supported radiobiological work in both of these aspects. Soon after WW II there were two general approaches to radiobiology, resulting from: 1) the aftermath of use of atomic weapons in the war, including resultant atmospheric nuclear weapons testing, and 2) radiotherapeutic cancer treatment. The RF followed both, demonstrating its long-standing concern with social and medical matters. But there was a much earlier involvement of the RF in radiobiology, dating from the 1920s as outlined above. Because of this long interest in radiobiology the importance of philanthropy in its history has now been clearly established

and this merits further study. It is hoped that a further period of study at the RA may produce further results of similar, or even greater, value.

As in most valuable research, findings often suggest further avenues for useful investigation - avenues of which the researcher was only partially aware beforehand (or even totally unaware). This was so in the present study and relevant examples including the pioneering role of the RF in establishing and supporting the earliest radiobiological research, both applied and basic. Also, the place of philanthropy in the history of radiobiology research merits further investigation. An indication of the prescience of the RF, incidentally noted, is that many of the researchers who were supported later became Nobel laureates. J.C. Bugher is an important contributor to the field of this study. His papers deserve a more thorough investigation, as do those of the others mentioned above. Similarly the records of the Rockefeller University's journal *The Medical Letter* deserve a more extensive examination than I was able to give in April 2009. Since the RAC contains so much material and many secondary documents, much effort and time was expended in finding the useful information, outlined above. For this reason it was not possible to study all the apparently relevant material and a proposal will be made to the RAC for an additional period of study in 2010.

In closing, I would like to mention that I am most grateful for the aid given to me by the RAC's archival and other staff. I am especially appreciative of their bringing to my attention valuable material of which I would have otherwise been unaware.

Endnotes

[1] International Education Board (IEB), Series 1.3, Box 54, Folder 858, RAC.
[2] Rockefeller University (RU), RG 303.1, Box 18, Folder Zirkle, RAC.
[3] RU, RG 450, Series 2.1, Box 6, Folder 2, RAC.
[4] Aaserud, Finn. *Redirecting Science: Niels Bohr, Philanthropy and the Rise of Nuclear Physics.* New York: Cambridge University Press, 1990.
[5] Kohler, Robert E. *Partners in Science: Foundations and Natural Scientists, 1900-1945.* University of Chicago Press, 1991.
[6] Pais, Abraham. *Niels Bohr's Times: In Physics, Philosophy and Polity.* New York: Oxford University Press, 1991.
[7] RU, Detlev W. Bronk Papers, RG 303-U, Box 28, Folder 12.
[8] RF, RG 1.2, Series 100, Box 9, Folder 65, Warren Weaver's Diary, February 28, 1958.
[9] RF, RG 1.2, Series 100, Box 9, Folder 65, Warren Weaver's Diary, March 17, 1958.
[10] RF, RG 3.1, Series 915, Box 3, Folder 24.
[11] RF, RG 1.1, Series 200D, Box 143, Folder 1760.
[12] RF, RG 1.2, Series 200, Box 138, Folder 1240.
[13] RF, RG 3, Series 915, Box 4, Folder 35.
[14] RF, RG 2, Series 100, Box 10, Folder 57, 1952.
[15] Willits, Joseph H. "Social Adjustments to Atomic Energy." *Proceedings of the American Philosophical Society* 90: 1, Symposium on Atomic Energy and Its Implications (January 1946), pp. 48-52. RF, RG 3, Series 910, Box 4, Folder 28.
[16] RF, RG R6 1.2, Series 400D, Box 1, Folder 5.
[17] RU, RG 303 U, Box 28, Folder 1.
[18] RF, RG 1.1, Series 101D, Box 43, Folder 55D.
[19] RU, RG 303 U, Box 28, Folder 7.
[20] RU, RG 12.2, Series Officer Diaries, Box 62, Folder Pomerat, 1951, Gerard R. Pomerat's Diary, December 18, 1951.
[21] RF, RG 12.2, Series Officer Diaries, Box 68, Folder Pomerat, 1948, Gerard R. Pomerat's Diary, January 1948.