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Biological basis of radiation protection needs rejuvenation

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Abstract

Purpose: Human beings encounter radiation in many different situations – from proximity to radioactive waste sites to participation in medical procedures using X-rays etc. Limits for radiation exposures are legally regulated; however, current radiation protection policy does not explicitly acknowledge that biological, cellular and molecular effects of low doses and low dose rates of radiation differ from effects induced by medium and high dose radiation exposures. Recent technical developments in biology and medicine, from single cell techniques to big data computational research, have enabled new approaches for study of biology of low doses of radiation. Results of the work done so far support the idea that low doses of radiation have effects that differ from those associated with high dose exposures; this work, however, is far from sufficient for the development of a new theoretical framework needed for the understanding of low dose radiation exposures.

Conclusions: Mechanistic understanding of radiation effects at low doses is necessary in order to develop better radiation protection policy.

Keywords

Biological effects of ionizing radiation; radiation protection; low dose radiation

Few reflections on the linear non-threshold (LNT) model

Radiation protection in the U.S. and most of the world is based on the linear non-threshold (LNT) model, introduced in 1966 by the International Commission on Radiological Protection (ICRP) (ICRP 1966). The LNT model, in its turn, relies on the linear quadratic (LQ) model of radiation damage. Most frequent use of this model in contemporary practice is for low dose radiation exposures where it is used to predict the unknown relationship between dose and stochastic biomedical responses (Biological Effects of Ionizing Radiation [BEIR] VII 2006; Hall and Brenner 2008). This model was designed to be used predominantly for radiation protection; at the time of its implementation it was considered unnecessary that this model would accurately explain biology at low doses. The model

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projects that any dose of radiation, no matter how low, can lead to a cancer regardless of biological repair mechanisms or other responses occurring in the human body as a whole at low doses. In essence, this model assumes that vastly different degrees of physical and chemical changes in living cells caused by radiation exposure (with doses distributed across six orders of magnitude) result in proportional and identical biological endpoints. From the standpoint of biology this is inappropriately simplistic. The LNT model was hoped to be sufficiently protective to handle unknowns in the low-dose range. Unfortunately, this has also led to misuses causing public concerns and undue sensationalism. For example, few studies looking at radiation doses from CT scans cumulatively rather than per patient claimed that this procedure will lead to hundreds of thousands of new cases of cancer (Kim et al. 2009; Redberg 2009; Smith-Bindman et al. 2009). Fortunately, appropriate applications of LNT (e.g. Pearce et al. 2012) still outweigh the misuses of this model.

Biological effects of low doses and medium and high doses of radiation do not differ in ‘volume’ but in quality

Studies from earlier low dose radiation research have documented novel processes at low doses that are not evident at high doses, e.g. different methylation patterns, different expression patterns for biomolecules with pleiotropic effects such as micro RNAs etc. (miRNAs) (Chaudhry et al. 2012; Bernal et al. 2013; Brooks 2015). Research over the past decade has demonstrated that many of the paradigms on which the current radiation protection standards are based may require change (Brooks 2015; Dobrzynski et al. 2015; Doss 2016; Sacks et al. 2016). Details on the history of the U.S. Department of Energy (DOE) low dose program are currently being published by the University of Washington (Pullman), authored by Antone Brooks, a previous Director of the DOE Low Dose program. This research, during the period of his supervision demonstrated that cells communicate with each other and that organs and tissues respond to radiation as a whole and not as single irradiated cells (Brooks 2015). This suggested that the ‘hit’ theory of cancer (Marte 2006a) – the prevalent cancer paradigm when early DOE radiation research begun (and the LNT model was introduced by ICRP) must be re-evaluated, particularly for low doses. A more recent understanding of carcinogenesis is that this process is far more complex than a pair of mutations (Marte 2006b) and genomic instability has been recognized as one of the critical issues in development of cancer (Eggleston 2006; Negrini et al. 2010). Once again, while medium and high doses of radiation produce genomic instability, this biological outcome is not equally certain after exposures to low doses and protracted low dose rate radiation (Kadhim and Hill 2015). Most ‘established’ carcinogenesis mechanisms are therefore absent from the list of low dose radiation exposure effects. For example, in areas of the world with high background of natural radiation these exposures have potential beneficial effects (Dobrzynski et al. 2015). Other so far not considered factors such as microbial flora modulate cancer incidence in general; this was found particularly relevant after low dose exposures (Clanton et al. 2015). Finally, some controversial reports suggest the existence of low dose hormesis in the low dose exposed A-bomb survivors/low dose exposure group of the LSS cohort (Doss 2016), although studies of the LSS cohort including all radiation exposures up to 3 Gy show mostly linear correlation between dose and cancer induction

(Ozasa et al. 2012). The fact that so many disparate views exist in the literature establishes that scientists are uncertain about the risks associated with low dose exposure.

The mechanisms involved in all these new paradigms require additional research to ensure that radiation standards are set based on the best possible science. With the loss of the DOE low Dose Radiation Research Program there is little new radiation biology (particularly at low doses) in the U.S. at this point in time. This is in contrast to ongoing work in Japan and the EU (Abbott et al. 2016) where new findings suggest a plethora of novel low doses responses. These new responses were identified primarily because of new technologies, improved sensitivities of old technologies, and large-scale databases analyses. These experiments point to new responses at low doses or local exposures that have not been previously identified as important – cardiovascular and cerebrovascular disease, developmental biology effects (embryo and new born), etc. (Bakshi et al. 2013; Hamada et al. 2014; Wang et al. 2014; Mancuso et al. 2015; Verreet et al. 2016; Subramanian et al. 2017); as well as studies on interactions between low doses of radiation and other ‘lifestyle’ exposures (Vares et al. 2014; Nakajima et al. 2016).

Misconceptions about how regulations are defined in the U.S. are found throughout the scientific literature. For a health factor to be detectable by epidemiological approaches, doses (and concentrations of chemicals) are usually much higher than those that would be permitted for the population. Most regulatory agencies examine cellular, tissue, and animal effects to gain a broad understanding of biological consequences at low and high doses and compare this to effects observed from epidemiological studies at moderate to high doses to make conclusions about risk effects of toxic agents. One problem that is perhaps more complicating for radiation effects is the dose-rate effect, which is even more difficult to examine in human populations where daily living patterns complicate conclusions from low dose effects. For example, the cancer risk from exposures to chemical carcinogens such as smoking overwhelms the effects of low dose radiation exposures (Kodama et al. 2012). Animal experiments, on the other hand revealed the ways in which, e.g. alcohol consumption and obesity modulate radiation responses in vivo (Vares et al. 2014; Nakajima et al. 2016). Thus, new ‘basic science’ research is necessary to inform us about sources of ambiguities and potential errors in epidemiological studies.

The area of controversy in the radiation arena revolves around doses that are 500 mGy and lower. However, while annual effective dose worldwide is 2.4 mSv on average (United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR] 2000), there are areas of the world with natural background radiation almost 10-fold higher with few detectable health consequences. Absorbed dose rate in air including cosmic and terrestrial radiation can be as high as 1.8 microGy/hr in areas with Monazite sands such as coastal regions of Kerala and Madras in India, or 17 microGy/hr (corresponding to 149 mGy/year) in Ramsar, Iran, due to radioactive spring waters (UNSCEAR 2000). Current regulations prescribe clean-up of radioactive waste sites to levels of 1 mGy/year or lower, an expectation that is costly and involves extensive labor. Nevertheless, the basis for this dose-limit is poorly justified by the science and thus may be unnecessarily rigid.

Recent work reviewed by the U.S. National Council on Radiation Protection and Measurements (NCRP) resulted in a report that is recommending a lowering of the regulatory dose limit for induction of cataracts. Contemporary methods for detecting cataracts have increased sensitivity and improved evaluation of radiation thresholds for cataractogenesis (Ainsbury et al. 2016). The new NCRP report asks for additional research and longer follow-up of those exposed to radiation. (Dauer et al. 2016; NCRP 2016). This development is emphasizing the need for more research to set improved dose limits for the public. Just as sensitivities for detecting cataracts have increased, approaches to detect other radiation-significant endpoints including cancer, cardiovascular disease, CNS disruption, cognitive effects, cell death pathways and more, became more sensitive as well. Single cell techniques have become feasible only recently such as, for example, single nucleus sequencing that allows investigation of small steps along the path toward malignant transformation (Navin et al. 2011). Such information may result in the need to either further restrict or relax current radiation exposure standards.

Biological effects of protracted and acute radiation differ in respect to life-shortening and cancer induction

Dose and dose-rate effectiveness factor (DDREF) is estimated from the dose-response relationships for acute and protracted exposures for similar doses (Ruhm et al. 2015). However, approaches to evaluate DDREF vary and two frequently considered values for DDREF are 1.5 (BEIR VII 2006) and 2.0 (ICRP 2005; Wrixon 2008). Many argue that mechanistic data from low dose exposures suggest that this number is underestimated (Brooks et al. 2016). In addition, computational techniques in recent years have also become infinitely more sophisticated and evaluation of large volumes of data easier with the new ethos of public databases and exchange of computational tools. Already, data sharing and improved data analysis have allowed for cross-comparisons of large-scale animal data from the EU and old archival datasets from the U.S. DOE's former studies (Haley et al. 2015). Findings of this study support a change in the way that DDREF is calculated; they do not support decrease of DDREF to the value of 1 which is, for example, currently proposed by Germany (Strahlenschutzkommission [SSK] 2014). Much more work is needed to answer these questions now that new statistical, computations and analytic approaches are available as well as new protocols for data sharing. Figure 1 (adapted from Haley et al. 2015) presents a comparison of life-shortening curves fitted to actual animal data from acute and protracted exposures (full lines) and the curve that would be calculated from the acute data alone (using the same approach that was used by BEIR VII and that is still currently applied on acute exposure data from A-bomb survivors) (Figure 1(a)). In addition, we compared goodness of fit for the same data and the current model (Figure 1(b)) and an alternative linear-linear model (Figure 1(c)). These data suggest that linear quadratic model for life shortening that is currently used as basis for LNT model is not robust enough to predict effects of protracted radiation exposures from acute radiation exposures alone. However, that assumption (that effects of protracted exposure can be extrapolated from acute exposures) underlies the linear quadratic model; for more detailed discussion please see Haley et al. (2015). Moreover, even when a direct comparison of acute and protracted exposures is done, simpler linear-linear model provides a better fit with the data.

In addition to life-shortening animal data, the BEIR VII report utilized animal cancer data to develop the final DDREF number estimate. In this effort, data selection was done without focus on solid cancers or lethal cancers (Figure 2); moreover, only the data from acutely exposed animals was used without an attempt to compare cancer incidence for acute vs. protracted radiation exposures of up to 2 Gy. This was justified by the notion that DDREF calculations were supposed to include low dose, and not only protracted low dose rate exposures; nevertheless, it is difficult to argue that the doses of up to 2 Gy can be considered 'low'. Inclusion of leukemia among these graphs was not replicating the situation that is under consideration for A-bomb survivor cohort where monitoring began several years after the exposure and many of the leukemia cases went unrecorded. However, probably the most important challenge of the dataset used is the fact that non-lethal cancers were included in analysis. If, for example, Harderian gland cancer graphs are removed from the Figure (right panel Figure 2), the most convincing curve fits are removed with them. Thus, it appears that the LNT-based DDREF calculations actually suit the non-lethal cancers best – a consideration that may have mechanistic biological implications.

New developments in cell and molecular biology should be used to deepen radiation biology of contemporary radiation exposures and rejuvenate radiation protection policies

In addition to the new low dose data and computational approaches noted above, new discoveries in molecular biology and medicine over the past 10 years include such prolific subjects as knowledge about reprograming and the use of stem cells, the role of exosomes and microvesicles in cell-to-cell communication on the level of the whole organism, the role of non-coding RNAs in intra- and inter- cellular regulation and many more (Pajonk and Vlashi 2013; Luzhna and Kovalchuk 2014; O'Leary et al. 2015; Sokolov and Neumann 2015; Flamant and Tamarat 2016; Al-Mayah et al. 2017). In addition, these newly emerging and existing areas have received an incredible boost by the introduction of techniques for a rapid transient gene expression modulation via silencing RNAs, as well as permanent genome modulation enabled by techniques such as CRISPR; bionanotechnology is also making significant inroads into daily biological (and medical) practice. Each one of these new developments opened new vistas in cancer research and other areas of medically oriented cell and molecular biology. A comparison of the molecules identified in biological signaling in 1996 with that in 2016 (Figure 3) reveals the new types of information that just two decades have provided. Molecules that were unknown 20 years ago are now at the forefront of studies in effects of toxins (including radiation) on cells and cellular function. For example, many studies have shown the importance of miRNAs in regulating gene expression in normal and cancer cells (Chaudhry et al. 2012; Luzhna and Kovalchuk 2014). At the same time, these techniques and information coupled with new types of animal irradiators can transport 'translational' research with model organisms through a minor revolution (Sakashita et al. 2010; Kong et al. 2016); in a recent example, chromosomal aberrations in mice were used to calculate the dose-rate effectiveness factor (DREF) (Tanaka et al. 2009). Research using these tools can provide a mechanistic basis for understanding of

the observations; paradigm changes are necessary in order to provide a sound scientific basis for regulations of the low dose exposures.

While OMICs and other technologies were available in the last decade, only a small amount of that information is being exploited for understanding low dose radiation effects. When such research is done, results are often surprising, suggesting, e.g. hormesis at low doses of radiation (Sokolov and Neumann 2015) or different responses to radiation when cancer cells and their normal counterparts are compared (Yang et al. 2016). Modeling and systems biology try at the very least to support the 'J shaped' cancer dose response and LNT at the same time (Lou et al. 2012; Calabrese 2015). Informatics and modeling-based approaches that are capable of exploiting new and existing datasets can be used to define low-dose effects in a more sensitive way because of the large volumes of data that can be used. There remain in the U.S. perhaps a few investigators who are involved in OMCIS research related to radiation biology, most through NASA-funded programs or focused on low and high doses of radiation both (Hyduke et al. 2013; Leszczynski, 2014; Reisz et al. 2014). While these researchers developed ingenious approaches for data analysis, and in the process made significant contributions to initiation of 'big data research', most of this work is becoming more and more constricted with the data input(s) becoming more limited, again, mostly due to the lack of foresight by the U.S. funding agencies. Fortunately, OMICs radiation work outside of U.S. has remained extensive (e.g. Pucci et al. 2015; Hauptmann et al. 2016; Subramanian et al. 2017).

Despite the lack of low-dose related funding in the U.S., radiation remains part of our daily environment, both natural and human-made. Human-made sources of radiation include radiation exposures to therapeutic and diagnostic X-ray sources and radionuclides, with diagnostic procedures contributing roughly 50% of the total dose to the population in America (Mettler et al. 2008; NCRP 2009; Goodman 2013), as well as production of contaminants of different military and industrial activities; for example, the U.S. Environmental Protection Agency lists 12 so-called superfund sites contaminated with radionuclides (Boyd 2016). Paradoxically, none of the grants sponsored by U.S. National Institutes of Health is dedicated to exploration of these sites considers radiation or radionuclides.

At this moment, the U.S. public does not know that the radiation standards now in place can be better, yet there is much fear and misinformation about radiation (Waltar et al. 2016). While a full grasp of this subject matter is difficult and requires critical thinking, better application of new knowledge, technologies, and approaches can only serve to enhance a more accurate, science-based and better-informed set of guidelines than currently exist. Here again, approaches and thinking developed in Europe and Japan could serve as inspiration for new efforts (Perko et al. 2016).

Specific research needs that should be considered in the development of a low dose research are as follows:

- Investigation of mechanisms by which cells detect and respond to very low doses of radiation;

- Investigation of differences between responses to low and high doses and dose rates of radiation at the molecular and cellular level, in tissues and whole body, considering also differences in routes for radiation exposure;
- Investigation of specific biological mechanisms involved in low dose radiation responses leading to protective and damaging cellular responses to different doses and dose rates of radiation;
- Additional focus on low dose-rate exposure models and experiments needed to produce data applicable to majority of contemporary human exposures;
- Use of recently developed techniques and approaches for data generation and evaluation;
- Accumulation and preservation of detailed data and materials to enable sharing of materials and information.

In summary, key points that can be made in support of a new low dose initiative on behalf of DOE and NIH are: (1) health effects of low dose radiation exposure remain ambiguous; (2) past work has set us on a good footing for the development of new studies; (3) policies regulating low radiation dose exposures rely largely on models developed for high dose and high dose-rate exposures; and (4) new technologies have not been sufficiently applied for low dose radiation research (especially in U.S.). Radiation protection policies worldwide need rejuvenation – research that could support this change needs to be an outcome of worldwide efforts, joint research and exchange of ideas.

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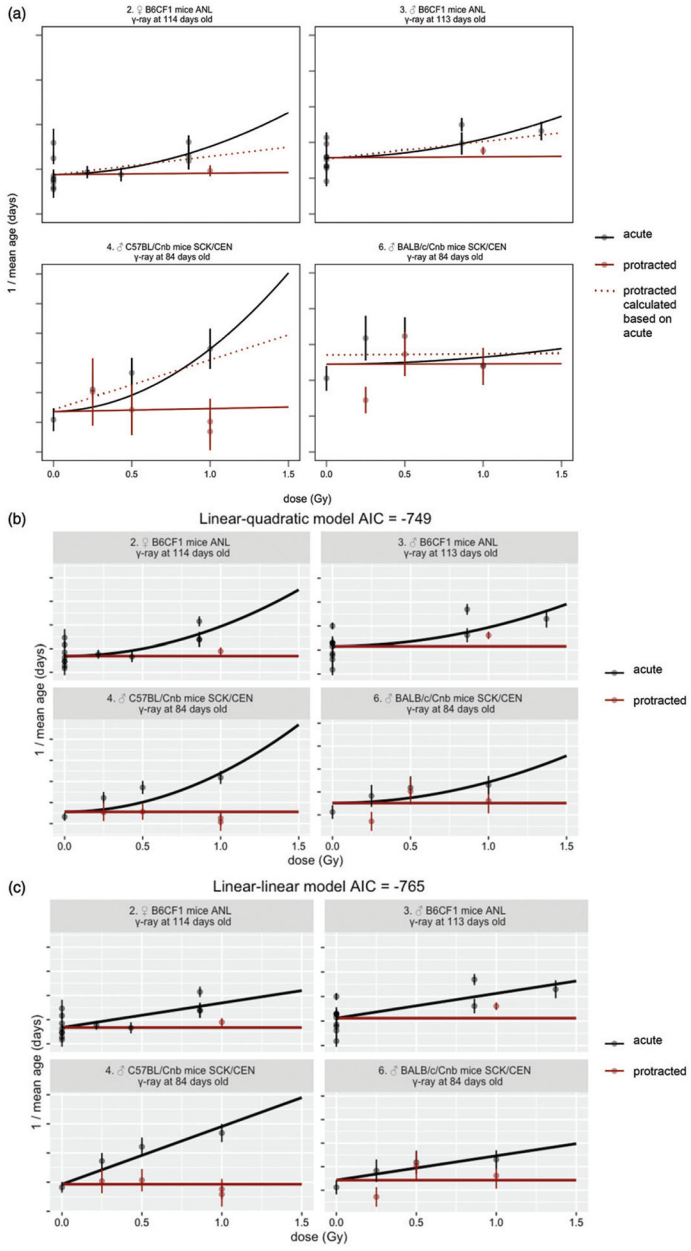

Figure 1.

Life-shortening data from mice exposed to acute and protracted radiation up to 1.5 Gy total dose, following BEIR VII procedure (for more details see Haley et al. 2015); currently used model based on linear-quadratic formula and alternative linear-linear model comparisons. Comparison of predicted life-shortening from protracted radiation exposures in a 0–1.5 Gy total dose range when only acute animal irradiation data on life-shortening is used to calculate DDREF (dotted red line) vs. when both acute and protracted data are compared (full lines) (a). In both cases calculations are based on BEIR VII approach, however, in one case (dotted red line) the graph is based on acute exposures, similar to extrapolations done from A-bomb survivor data. In the other case, calculation is done considering both acute and protracted dose exposures, and the graph of life-shortening associated with protracted

exposures is shown by a full red line. Moreover, a simpler liner-linear model provides a better fit with the data than the currently used linear-quadratic model. The Akaike Information Criteria (AIC) estimates appear above each fit and quantify the goodness of fit: a lower value indicates a better fit. Overall AIC value for linear-quadratic model (−749) (b) is greater than the AIC value for liner-linear model (−765) (c), indicating that the linear-linear model fits the data better.

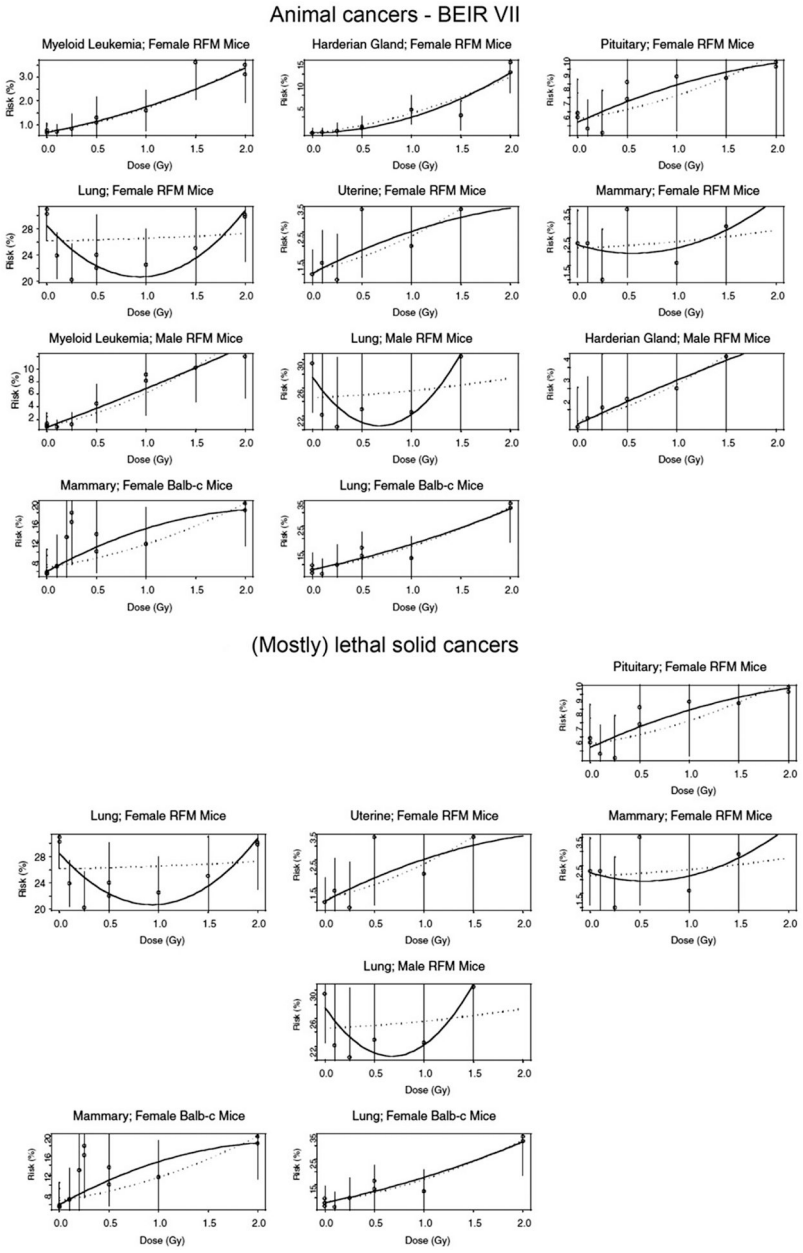

Figure 2.

DDREF calculations for cancer risk with increased dose of radiation up to 2 Gy done by BEIR VII based on animal cancer data should be reconsidered. Top panels - original BEIR VII graphs include a mix of leukemia and solid cancers as well as a mix of lethal and non-lethal cancers. A DDREF calculation was done for these data summarily leading to the calculated DDREF value of 1.3. Bottom panels depict the same graphs but only for solid cancers, and exclude non-lethal cancers such as Harderian gland cancer. Moreover, lung cancer data used by BEIR VII includes some benign pulmonary adenomas. If these more limited data were used, the DDREF calculation outcome would be different. In other words, DDREF recalculation requires careful data pruning and direct comparisons for acute and protracted data as it was done for life-shortening in Figure 1.

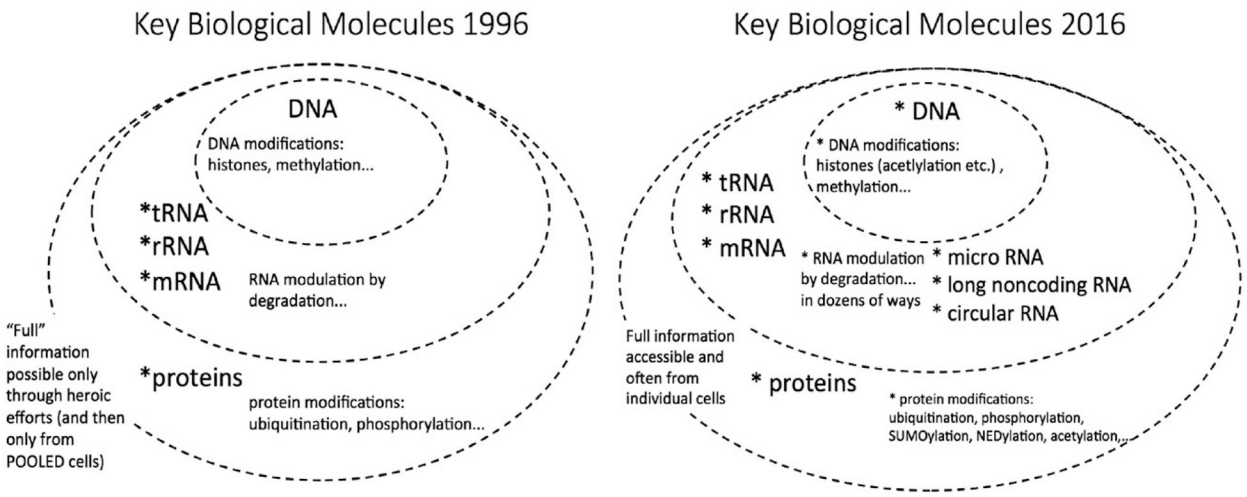

Figure 3.

Progress in molecular biology over the past 20 years focusing on nucleic acids and proteins and their modifications.