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NOTE

Throughout this report and its annexes cross-references are denoted by a letter followed by a number: the letter refers to the relevant technical annex (see Table of Contents) and the number is that of the relevant paragraph. Within each technical annex, references are made to its individual scientific bibliography by a number without any preceding letter.

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ANNEX F

FUNDAMENTAL RADIOBIOLOGY

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I. DISSIPATION OF PHYSICAL ENERGY
(Space and time factors)

Introduction—Direct and indirect effects

1. The effect of radiation is induced by the processes of absorption, when the energy of radiation is dissipated in the irradiated matter. Apart from excitation, the ionization of molecules is believed to be largely responsible for the initiation of primary chemical reactions. There are at present two major theories of the mechanism of action of radiations on living organisms: the theories of direct and indirect action. The first one claims that effective ionizations take place *in* key cellular structure or in their immediate vicinity: the probability that their alteration causes cellular damage is dependent on their biological specificity. This has often been called the "target theory", and, since Dessauer, Crowther, Holweck and Lacassagne, Timofeeff-Ressovsky and Lea, the concept has had the support of many physicists; it is being constantly revised to take into account many new fundamental acquisitions.[1,2,3,4,5,6,7]

2. The "theory of indirect action," on the contrary, claims that the biologically specific cellular structures are altered as a result of their chemical reaction with free radicals formed in irradiated water or other molecules not belonging to these structures.[8] As with most conflicting theories which have had ardent supporters on both sides (another good example is the corpuscular and electromagnetic theories of light), it is very probable that the two are complementary. Indeed, it is almost certain that the same cellular component can be affected in a way which is liable to produce identical biological effects by both mechanisms.[9,10,11] Methods have been

developed in recent years which enable the existence of unpaired electrons resulting from the ionization process to be demonstrated not only in crystalline amino acids and other small molecules, but also in proteins, plant embryos and other kinds of cells.

3. An attempt will be made to draw a brief picture of some fundamental aspects of the problem.

Linear energy transfer (LET) and relative biological effectiveness (RBE) of different kinds of radiation

4. The efficiency of radiation *per ionization* to induce a particular effect is often found to vary for different types of radiation. Let us at first consider an event which is caused by one ionization such as the inactivation of an enzyme or virus: in the case of small structures *in vitro*, the radiation producing a low ion density will be more effective than that giving a high ion density, because some of the ionizations of the latter will be wasted. On the contrary, a radiation with a high density of ionization will be more effective when several ionizations are simultaneously or in a relatively short time needed in the sensitive structure. Thus, the *relative biological effectiveness* (RBE) of radiations varies with their *linear energy transfer* (LET). This term describes the spatial distribution of the transfer of physical energy in matter—and accounts for the loss of energy of the radiation, not only through ionizing processes, but also through other processes such as dissipation of heat or excitation of atoms. It is a theoretical implication of these facts that some of the primary effects of radiations take place within a shorter time than that needed for the processes initiated by ionization or excitation to lose their initial spatial distribution (perhaps as short as 1 millionth of a second); and also that the primary biological receptors of radiation are not themselves homogeneously distributed throughout the cell.[12]

5. In mice, the relative biological efficiency (RBE) increases greatly with ion density, for killing with low intensity radiation, for shortening of the life-span, for inhibition of tumour growth, and for cataract induction; the increase, however, is smaller when one considers effects on the gonads (sterilization), on the skin (epilation), on the blood white-cell count, or on the induction of many chromosome abnormalities in Drosophila.[12,14,15] Some chromosome abnormalities in Tradescantia have a very high incidence with high density irradiation.[13] Mutations in micro-organisms and some in Drosophila are only slightly influenced by the LET.[12]

6. Reviews on the subject by Lea[1] and Zirkle[12] have shown that much could theoretically be achieved by comparing the effects of ion density. Lea had attempted to use the data available to him at the time, on the decrease in incidence of chromosome breakage with decreasing ion density, as an argument for the target theory. However, it appears from Zirkle's paper that changes in RBE for comparable effects are often very difficult to include in a general theory, because in many instances the direction of change in RBE is not the same for similar effects in different materials and the RBE may be strongly dependent on conditions of irradiation such as the oxygen tension. It is at present very difficult to make definite generalizations.

7. The mode of dissipation of radiation energy inside living cells is not yet understood, although our knowledge of the physical aspects of energy loss is adequate and hypotheses on the distribution of free radicals along the radiation tracks have been suggested. However, it is not clearly understood how this physical energy becomes apparent in chemical changes such as ionization and excitation. It might be of interest to use inert structural models or do such experiments as comparing the LET for a virus inside and outside the host cells to get a better picture of the sequence of events. When completely understood, the use of radiations of different LET may lead to precise estimates concerning the size of the biological structures affected.

Dose-effect relations

8. When a homogeneous substrate is irradiated, the energy is distributed in an unpredictable way and the probability of a molecule being hit depends on its concentration and on its volume. The concentration of the intact substrate decreases as radiolysis proceeds, and it can be predicted on theoretical grounds for low density radiations that, if one ionization suffices to cause the effect, the expression relating the remaining intact structures ("survivors") to dosage will be *exponential*. When a relatively small number of ionizing events is needed, the number of responses observed will, however, be approximately proportional to the dosage.[16,17,18] This sort of effect has no *threshold*—which means that any dosage, however small, is effective in producing some alteration.

9. On the contrary, if several ionizing events or "hits" are needed, the response only becomes manifest after a certain dosage has been accumulated in the sensitive structure: the dose effect curve is then *sigmoid*.[16,17,18,19] In this case there is a *threshold* which, however, may only be statistical, as when two identical cellular structures need to be *irreversibly* altered for the effect to become manifest, which is so for recessive lethal mutations in yeasts.[16] Other threshold effects appear when recovery of the altered structure or replacement of killed cells takes place, as is often the case in multicellular organisms where many interferences may take place between the primary physical event and its biological expression.

10. The meaning of the dose-effect relationship is often difficult to understand because the curve may change quite dramatically when the conditions of irradiation are altered (aerobic or anaerobic irradiation; change of culture medium); this difficulty is most likely to occur when one studies a complex phenomenon like cell death, whose cause may be multiple and not identical in different circumstances.[20]

11. However, several radiobiological processes are known to give exponential dose-effect curves under specific environmental conditions, as in the case of many lethal effects on viruses and on micro-organisms.[21,22] Diploid yeast cells[19,23] or mammalian cells[24] in tissue culture have a sigmoid dose-effect curve when x-irradiated. In the case of diploid cells, the sigmoid type of curve is consistent with a 2 hit process, the exponential response being explained on the assumption of a single hit. One of the best present arguments for the "target" concept comes from the fact that in the case of small viruses the "target" size can be estimated with a good approximation[21] and that survival curves of protected bacteriophage are very similar *in vitro* and during the very first minutes of infection.[22] These results can be

explained on the basis that the primary ionization takes place inside the sensitive structure. In the case of a mutation this is the gene. It is, however, difficult to accept the concept without modification at the present time, on account of the possible contribution of diffusable radicals from water or other molecules in the immediate vicinity of the target. However, it is believed that radicals only diffuse for distances of about 30Å. As most effects have not been fully expressed when the radiation has ceased to be delivered, there is a time interval during which restoration may occur, and whether this takes place or not may alter the dose-response curve. Very little is known about what happens during this time: the chain of events may be relatively "simple" in the expression of a point mutation in micro-organisms or perhaps even in a mammalian germinal cell, but it is certainly very complex when the induction of malignant growths is considered. The number of *mutations* in bacteria,[21] Drosophila,[25] and perhaps mouse populations,[26] *increases* linearly with radiation up to moderate dosages, as do certain of the chromosome aberrations[27] and perhaps the induction of leukemia.[28,29] However, the determinations do not extend as low as the background radiation, and much uncertainty remains at these low levels, although it is highly probable that the background radiation causes some of the mutations which occur naturally, thus contributing to some extent to the evolution of living organisms and to their load of mutational hazards. *This means that as far as we know at present, biological effects will follow irradiation, however small its amount.* It has thus become very important to establish with great accuracy the shape of the dose-effect curve in the lower dose range, in order to estimate the contribution of the natural radiation for different effects. The number of experimental animals needed to obtain a good accuracy increases enormously as the dose decreases and the response becomes smaller or less frequent. For human populations, as each individual is important, the only reasonable "experimental sample", when small doses are concerned, is the total population of living human beings. In this case, the only sound procedure is to get a better understanding of the fundamental processes which are occurring. *This may actually be the only way of answering some of the basic problems underlying low dosage irradiation.*

Time intensity factor

12. The time taken to deliver a given dosage of radiation can be varied in order to give very high or very low *intensities* per unit time. A change in intensity will not affect the end result when separate ionizing events contribute *independently* to the observed effect; this should hold true for some of the exponentially responding events although it is not true for all. On the contrary, in the case of events responding by sigmoid curves, several ionizations may be needed almost *simultaneously* (this is the case when recovery processes exist); here, a given dose becomes less effective if delivered in a long interval of time.[31,32,39] However, this is not always the case, and for inactivation of both homologous chromosome regions of a diploid cell, it is known that protraction of irradiation does not alter the effect.

13. The physiological conditions of *Drosophila* sperm are very constant for a considerable length of time, and it has been found that the induction of mutation by irradiating the males does not vary with the intensity of irradiation.[30] The same is true for the induction of most malformations in the mouse embryo. However, in some cases the severity of malformations is *greater* if a given dose is fractionated.[33] A change of intensity by a factor of one million does not alter the number of phage induced in E. Coli.K_{12}.[37,38] In contrast, the number of certain chromosome aberrations in Tradescantia microspores or Vicia seeds[34,36] — like chromosome exchanges, which require the simultaneous occurrence of two breaks —are often highly dependent on the time taken to deliver the dosage: more exchanges are obtained for higher intensities. When the duration of irradiation is increased, one reaches a time for which the effectiveness does not decrease any more; this time is related to the lapse during which the breaks remain open. However, this picture is complicated by the fact that the rate of rejoining depends on respiratory activity.[35] The killing of complex organisms like mammals, being the result of extremely complex cellular damage, is very efficient for high intensities but much less so for low ones.[40,41,42]

14. The time during which radiation is delivered becomes very important if the system being studied undergoes some *change* during this time: the radiosensitivity of many cellular processes varies during the *mitotic cycle* and one can expect a greater radiation effect if the intensity is high during the most sensitive period of this cycle. Secondary biological reactions may interfere with the expression of damage and, if recovery or selection occur, one can expect a greater effect if the intensity is high for the same given dosage. For these reasons, *it does not appear justifiable, unless the fundamental pathways of radiation damage are known, to consider that an effect observed after high intensity irradiation will necessarily follow the application of the same dosage at low intensity.*

Inactivation by transmutation of radioactive elements

15. Certain radioactive substances taken up by the organisms in specific structures may affect them not only by the radiation they emit, but also by the fact that the emission of these radiations is often accompanied by recoil effects or transmutation into an atom having new chemical properties. Thus P-32 can be incorporated into important biological structures like viruses or chomosomes, and in the first case it has been shown that the inactivation due to transmutation of P-32 into S-32 is more efficient than the one due to the β particles being emitted.[44,45] It is conceivable that strontium could replace calcium or magnesium, which are probably structural constituents of chromosomes.[46] It has been claimed that a low calcium environment increases the number of spontaneous and induced chromosome breaks in Tradescantia.[47,48] If these facts were of general application, the disintegration of strontium-90 or strontium-89 might affect cells not only by emitting β radiation, but also by transmuting to yttrium, which has new chemical properties. Such possibilities will have to be discussed, and *the role of trace amounts of metals and of alkaline earths in important cellular structures should be known before one dismisses its possible importance in biological effects of radionuclides which, apart from emitting radiation, have a specific function.*

16. Although Ca-45 has not been found by radioautography in the bone marrow cells of rats previously injected with 200 μc,[49] nuclear aberrations have been observed in allium which had been grown in the presence of Sr-90,[50] and further work on the subject should be done to settle this problem, which is of great importance in understanding the possible cellular damage induced by radionuclides. Their specific radioactivity inside cellular structures as well as their rate of turnover and their

chemical function may be important in inducing cellular damage.

II. Radiation chemistry

17. It is only by understanding the mechanisms of action of radiations on the different cellular constituents that one can hope to understand what is happening in irradiated cells and also to use these basic findings in the search for protecting agents. Much useful information on the chemical effects of radiation has been gathered by submitting various chemicals to irradiation *in vitro* (radiation chemistry); however, on account of our very incomplete knowledge of cellular structure and chemistry, biological constituents should be studied after irradiation of the living organisms (radiation biochemistry) if one is looking for full understanding of radiobiological processes. Furthermore, as will be pointed out, specific constituents and not bulk chemical properties should be studied whenever possible. Molecules may be altered by *indirect* and *direct* effects of radiation.

Indirect effects

18. It is known that the most abundant of all biological constituents is water: it constitutes 70 per cent of most living cells except for certain plant seeds and may sometimes constitute more than 95 per cent, but an unknown proportion of it is bound water and constitutes part of the cellular structures. This has prompted much research into the radiochemistry of water.

Effects of radiation on water and substrates in aqueous solution[51,52]

19. It is usually accepted, although by no means demonstrated, that water when chemically pure undergoes ionization and, as a result of this—and of secondary reactions, the sequence of which is hypothetical—splits into OH^0 (hydroxyl radicals) and H^0 (hydrogen atoms), which recombine; in the absence of any impurity, nothing apparently will have happened because the radicals cannot enter any other reaction. Traces of H_2 and H_2O_2 are thought to be formed during this process. The formation of radicals takes place in the short time of 10^{-11} -10^{-12} sec.[53]

20. The existence of OH^0 radicals has been demonstrated: certain radiation reactions leading to the polymerization of acrylonitrile can best be explained on the basis of an OH^0 radical mechanism, as also the oxidation of benzene to phenol.[51,52]

21. On the other hand, the existence of free H atoms is still questioned on account of the high oxidizing power of radiation on substrates in aqueous solutions; several mechanisms of radiolysis have been suggested, which do not make necessary the postulation of the existence of H^0 atoms.[51] It may be easier to interpret many biochemical reactions of radiation when a better understanding of the radiolysis of water has been achieved. This should certainly be of great importance for the logical approach to protection mechanisms. Although the existence of a free hydrogen atom is doubted by some, many authors have assumed that it does exist, and much present thinking is based on this assumption. It will make the discussion easier if we tentatively adopt this view, whenever a mechanism involving this radical is suggested. If oxygen is present as it is when a solution is in equilibrium in air, O_2H^0 (perhydroxy radical) and H_2O_2 (hydrogen peroxide) are also formed in addition to H^0 and OH^0.[51]

22. When the water contains various solutes, these are the site of chemical reactions due to H^0, OH^0 and O_2H^0 radicals formed in the solution through the radiolysis of water. These radicals have reducing or oxidizing properties and can react with the substrate, oxidizing or reducing it or transforming it in turn to a new free radical. Thus, if many solutes are present, they may be altered by radicals coming either from water or from the other solutes; this last mechanism although not too well studied could very well be of some importance in very complex systems. When macromolecules are irradiated, the yield of altered molecules per ion is usually smaller than expected from what happens to smaller molecules of similar chemical properties; this is thought to be due to the fact that bonds, broken in these structures, are not able to come apart (they are held together by the other intact bonds in the structure or cannot come apart by normal diffusion processes) and the radicals formed presumably recombine. Such a "cage effect" would be chiefly expected in concentrated solution and in complex cellular structures.[54] There are probably also some biologically inert chemical groups whose alteration would not impair the biological activity of some macromolecules.[55]

23. Although some reduction reactions occur when substrates are irradiated, most reactions appear to be oxidative.[52,56] From experimental data it is apparent that a substance is reduced only when it possesses a very high normal redox potential (greater than 0.9 - 1.0 for effects of X-rays in the absence of oxygen).[57]

Nature of the chemical effects

24. Ionizing radiations may alter inorganic as well as organic substrates. The following reactions can be taken as examples:[51]

Oxidizing reactions may be effected by OH^0 radicals

(*a*) By simply removing an electron from an ion $Fe^{2+} \rightarrow Fe^{3+}$—a reaction used for chemical dosimetry;

(*b*) By removing an H atom, leaving a radical which can combine with another one[51]
$2CH_2\,COOH \rightarrow 2C^0H_2\,COOH \rightarrow COOH\text{-}CH_2\text{-}CH_2\text{-}COOH$;

(*c*) By substitution of a hydrogen by an OH^0 as in the oxidation of benzene to phenol.[51,58]

25. In a similar manner, small organic molecules like alcohols, aldehydes or acids undergo oxidation, and the last-named compounds are often decarboxylated.[51,59,60] They are also sometimes capable of undergoing polymerization by the formation of a chemical bond possibly between two radicals as in the second reaction above: acetic acid is capable of giving succinic and even still more complex organic acids. Amino-acids may be oxidatively deaminated,[51] and if they have sulfhydryl groups these are oxidized to disulfur (S-S)[64] and sometimes to sulfoxide, as in the case of cysteine.[60,61]

26. *Reducing reactions* may be obtained as follows:

(*a*) OH^0 radicals may act on strongly oxidizing agents (this is the case for iodate and ceric salts).[51]

(*b*) In certain cases, organic redox indicators have been reversibly bleached in the absence of oxygen.[62] The mechanisms are at present difficult to understand on account of the questionable existence of the free H atom.

(*c*) Coenzyme I (Diphosphopyridine nucleotide) can be reduced by radiation to an abnormal derivative (probably a dimer of the natural molecule) but only in the presence of a hydrogen donor like ethanol.[63]

27. *Complex molecules*, such as enzymes and other proteins,[65] nucleic acids, lipids and polysacharides, are also altered *in vitro* as a result of the action of ionizing radiations; enzymes and desoxyribonucleic acid (in the case of the transforming principle of bacteria) may lose their biological properties.[68,69] In most cases the nature of the reaction has not been analyzed and cannot be until we know more about the structure of these macromolecules.

(*a*) One of the most sensitive chemical groups of proteins is the sulfhydryl group (-SH): two adjacent groups are oxidized by OH^0 to -S-S resulting in the loss of biological activity when, as in some enzymes, this activity is associated with the reduced form. S-S bridges also cause cross-linking reactions between two adjacent molecules.[65,81]

(*b*) Other specific oxidation reactions of some macromolecules have been found, including the deamination or decarboxylation of proteins,[66] and the oxidation of structures containing double bonds, as in the case of unsaturated fatty acids;[66] but large dosages have usually been necessary in order to make measurements possible.

(*c*) Cross linking may occur through the formation of a carbon to carbon linkage as the result of the combination of two macromolecular free radicals, possibly formed by direct or indirect action.[71,72] This process has, however, mostly been studied in artificial high polymers like polyvinylalcohol, but it is also very likely to take place in cells where the local concentration or the orientation of macromolecules relative to each other may be advantageous for such a process, as in chromosomes or during the formation of other oriented cellular structures. There is in fact good evidence for its occurrence in protein[73] and in DNA.[74]

(*d*) Some effects of ionizing radiations on complex molecules of biological interest have been definitely shown to be due to OH^0 radicals: this is so for the inactivation of ribonuclease, carboxypeptidase or the SH enzymes. These effects can be duplicated by chemically produced OH^0.[75] In the case of bacteriophage S_{13}[76] or catalase,[78] however, it has been suggested that they become inactivated as a result of a reducing mechanism but, on account of the problematic existence of independent H atoms in usual conditions of irradiation, one can probably not be certain of the exact mechanism, since new experiments[77] may yet lead to other interpretations. In many cases the mechanism of inactivation has not been worked out.

(*e*) The physical chemical properties of these molecules may be altered: the asymmetry of nucleic acids,[66,67,70] of fibrous proteins[80] or of hyaluronic acid[79] may be decreased, possibly but not necessarily as a result of a depolymerization; the absorption spectrum of these various compounds is often altered, indicating a chemical alteration of the chromophore group;[75] the stability of proteins and nucleic acids towards heat or other denaturing agent is usually decreased.[70]

Direct effects

28. In the case of a *direct* effect,[1,52] the ionization caused by the radiation concerns the molecule or structure under study. It is probable that the energy released in one part of such a molecule will be transferred over the whole structure and ionization or excitation phenomena will not necessarily occur at the point of first interaction. If the molecule becomes ionized, reactive free radicals may be formed and the existence of unpaired electrons has been proved in experiments using paramagnetic resonance; in the absence of water, these radicals are found to exist for periods as long as weeks or months.[83,84] In the case of water solutions, the life of the radicals is much shorter (a few minutes). Such studies have also been made in irradiated cells, indicating the existence of free radicals.[84,85]

29. Cross-linking between macromolecules may occur, as in polyethylene, probably by the reaction of an ionized molecule on a normal one.[86] The absence of an electron from a chemical bond may make this bond unstable and cause it to be hydrolyzed or broken, and some ions may also react with normal molecules causing them to cross link, as in some synthetic polymers.[73] The absorption of energy from the ionizing radiation does not always result in the expulsion of an electron: when ionization does not occur, the group of atoms may become *excited* for a period perhaps as short as 10^{-8} sec. thus being rendered more reactive with other molecules and susceptible to chemical alteration.[87] Excitation is the only process responsible for the alteration of substances by ultraviolet or visible radiations, and the use of these types of radiations is thus extremely useful in this respect.

30. *The physical state of a protein molecule* can be made to vary, and it has been shown that when an originally globular protein like pepsin is unfolded at an air-water interface and is irradiated as a monomolecular layer it is much more sensitive than when the "stretched" molecules have been compressed into fibres.[88]

Distinction between direct and indirect effects

Dilution effect

31. It is possible to distinguish between direct and indirect effects in a simple system by increasing the concentration of the molecules under study. In the case of indirect effects, the yield of altered solute molecules decreases with increasing concentration of the solute.[89,90] It has thus been calculated that in a 1 per cent solution of the enzyme carboxypeptidase, more than 90 per cent of the inactivation is indirect; in a 20 per cent solution, only 60 per cent of the effect is indirect.[90]

Desiccation and protection

32. One can also obtain information on the relative importance of direct and indirect mechanisms by comparing the yield of a radiation reaction on the same substrate after desiccation, in a completely protected solution and in the absence of any protector, although it is probable that one will not be able to secure absolute protection against indirect effects.[91]

Temperature coefficients

33. One can expect, if diffusible free radicals play a part in the *indirect* effect, that the contribution of this type of effect could be reduced considerably by freezing the solution.[92] This has been experimentally proved. However, irradiation of dry substances at different

temperatures shows that the *direct* effect of ionizing radiation also varies with the temperature, which makes the use of temperature coefficients more hazardous, but nevertheless useful.[82]

Oxygen effect

34. The existence of an oxygen effect (paragraph 38) was considered until recently as a criterion for indirect effects; however, as the radiosensitivity of dried proteins and polymers varies with oxygen tension,[93,94] this is no longer a good test until more is known about the mechanism of oxygen effects.

35. A major problem in radiobiology is to determine the relative contribution of direct and indirect effects[3] and its solution will also be of great help in developing methods of chemical protection. A first attempt has been made with yeasts; it can be shown that when they are irradiated in the dry and hydrated state the order of magnitude of both types of effects is very similar.[95] However, the molecular organization of most structures (chromosomes, cytoplasmic particles, nucleoli, cell membrane) is hardly understood, nor is the contribution to these structures of free or bound water and the possibility of diffusion of the free radicals formed during irradiation into or around them. A better understanding of all these fundamental problems would undoubtedly be of great value.

Effect of LET

36. According to the type of radiation used, yields per ion pair formed may vary as a result of different LET. It has been calculatted for water solutions that radiation giving high specific ionizations (α particles, slow neutrons, soft electrons) produce high concentrations of H^0 and OH^0 radicals along the ionization track;[96] their efficiency per ion pair in water solution will thus be smaller, when they are compared to γ or x-rays or high energy electrons. In the first case, the radicals, being more densely distributed in space, will have a higher probability of recombining or neutralizing each other, and this explains the lower yield of reactions such as the oxidation of tyrosine, the inactivation of the enzyme carboxypeptidase or of several viruses when the high specific ionizations are used.[12]

37. These densely ionizing particles form H_2, O_2, H_2O_2 and presumably HO_2^0 as a result of the radiolysis of H_2O_2 in water, *even in the absence of oxygen* and there are instances where H_2O_2 has been shown to be responsible for part at least, of the effect of these particles; it has been estimated that local concentration of H_2O_2 may reach molarity along the track of α particles.[96]

Oxygen effect

38. In *aerated* water solutions, irradiated with X or γ rays, H_2O_2 is formed, and it is thought that the radical O_2H^0 (perhydroxyl) is also produced as a result of the reduction of molecular oxygen by an H^0 atom;[51,97,100] in these, the radio-oxidation yield of many substrates is strikingly increased, sometimes by a factor of 3 to 6. In the case of the more densely ionizing particles, as these radicals are formed even in the absence of oxygen, one finds hardly any oxygen effect.[51,98,99] In some instances, new oxidation products appear, as when irradiated alanine becomes oxidized to pyruvic acid[101] (the latter also occurs as a natural oxidation product of alanine through the action of aminoacid oxidase).[51] In some degradation reactions of polymetacrylate, oxygen is necessary;[97,102] organic hydroperoxides or peracids also arise by the oxidizing action of O_2H^0 on organic acids.[51,103,104] The rate of inactivation of certain non-SH enzymes does not appear to depend on the presence of oxygen, but SH enzymes are far more radiosensitive when oxygen is present.[105] Other biological materials such as the desoxyribonucleic acid[67,68,102] or bacteriophage[76] (a desoxyribonucleoprotein) appear to be inactivated by ionizing radiations, by mechanisms chiefly independent of the presence of oxygen. This is also true for the induction of bacteriophage in E. Coli K12.[37,106] But it has been shown that DNA irradiated in the presence of oxygen is capable of forming hydroperoxides which arise almost certainly from the indirect effect of the perhydroxyl radicals on pyrimidine bases.[107] However, the excited DNA molecule itself can form similar compounds by reacting with molecular oxygen and this will result in the direct formation of hydroperoxides.[108] It has recently been shown that *dehydrated proteins* (trypsin) *also show an oxygen effect* when irradiated with sparsely ionizing radiation (X or γ rays); this may be due to O_2^- ions.[93]

After-effects

39. It has often been observed that the molecules under study continue to undergo alteration *after* the exposure to irradiation has ceased. This is the case for the oxidation of tyrosine,[109] or for the inactivation of some proteins,[110] nucleic acids,[67] bacteriophage,[111] other nucleoproteins[113] hyaluronic acid.[79] Pneumococcal DNA when tested for transforming activity does not appear to show any after-effect after irradiation in 1 per cent yeast extract.[68]

40. The after-effect seems to be the result of a primary process taking place chiefly in the presence of dissolved oxygen but it may not be sufficient in itself to inactivate the molecule. It could be due to the H_2O_2[111] or to the organic hydroperoxides[112] formed in the solution, but other hypotheses have been presented.

41. The case of desoxyribonucleic acid has been the most studied: many mechanisms—such as the oxidative formation of labile phosphate links with the sugar rings of the macromolecular chain or the slow unwinding of the double helical structure of desoxyribonucleic acid—have been postulated.[114,115,116] Although H_2O_2 formed in the solution does not appear to be necessary in the case of desoxyribonucleic acid,[116] it may have a very pronounced effect on bacteriophage S_{13} which becomes more sensitive to this agent after irradiations; S_{13} also becomes more sensitive to some reducing agent like ascorbic acid.[76] As the after-effect does not appear to occur after irradiation in the dry state (in the case of DNA)[55] it does appear to be the consequence of an indirect effect of irradiation. One will not be able to estimate its contribution in irradiated organisms until one knows more about direct and indirect action *in vivo*.

Radioprotection

In water solution

42. In a radiation-induced reaction taking place in water, the fact that the major part of the effect is of indirect origin has fundamental as well as important practical consequences.

43. Any other solute, reacting with the free radicals formed at the expense of the water molecules, will render them less available to the substance under study and protect it possibly by a competitive mechanism.[8,117] Many organic or inorganic compounds are efficient *in*

vitro, amongst these thiourea, aniline, phenol, cysteamine and its oxydation derivative cystamine,[97] and S-2-Aminoethylisothiuronium° Br°HBr (AET).[118]

44. Substances capable of reacting with essential groups of enzymes may, when present during irradiation, protect the group; removal of the agent after irradiation uncovers an unaltered group and this has been shown to be the mechanism in the case of SH enzymes protected *in vitro* by some SH reagents.[65,119] Many enzymes are also protected by their substrate,[120] their coenzyme or by competitive inhibitors,[121,122,123] probably also because the biologically active sites of the enzyme molecules are masked by the protector. It has been suggested, furthermore, that the SH group of cysteamine can protect SH groups of enzymes by becoming linked to them reversibly through S-S bridges. Similar dissociable complexes can be postulated in other instances.[124,125]

45. If organic radicals originating from irradiated molecules are prevented to diffuse from one another, one favours their rejoining. This is also a possible mechanism of radioprotection and it can probably be achieved by freezing at *low temperature*.[126]

46. Reducing the oxygen tension will inhibit those effects of radiation which are known to be increased in oxygen. There are many ways of producing anoxic conditions, including the use of chemicals, such as hydrosulfite, cysteine or cysteamine,[127,129] and of more usual respiratory inhibitors. *In vivo*, many reducing organic substrates which consume the cellular oxygen by way of the normal respiratory processes probably also produce anoxic conditions.[20,128] It is difficult at present to know the exact contribution of these mechanisms in the case of certain protecting agents like cysteine or cysteamine; it is probable that it varies according to the type of substrate, the presence of other solutes and the concentration of the different substances.

In the dry state

47. However, it is possible to protect molecules in the dry state. It has been shown that the four first substances listed above, (paragraph 43) when incorporated into a synthetic polymetacrylate, protect it during irradiation even when in the dry state.[55] In the solid state, no water radicals being present, the protective action is probably due to a transfer of energy through the polymer molecules to the radioprotector. This would be the mechanism of protection in the case of a *direct* action of radiation on the molecule. The ribonucleic acid of tobacco mosaic virus also appears to be protected against direct effects by cysteine.[130]

Restoration

48. Restoration is a process starting in the irradiated material, by which the original product can be obtained with its normal characteristics.

49. Reducing agents when added after irradiation have been shown to be capable of restoring the full enzymatic activity of a number of SH enzymes. The restoration is complete only at very low dosages; as dosage is increased, reversibility is less and less complete, which shows that different sites of one molecular species are altered with different efficiencies.[65]

50. Although some compounds are normally oxidized or reduced during normal cellular processes, the radiobiological oxidations or reductions may lead to a product which is not the natural one and which cannot be restored to an active biological compound by natural processes.[63] Coenzyme I *is reduced* by X or γ irradiation to an unnatural product only in the presence of alcohol which is oxidised to acetaldehyde; the reaction cannot be reversed by enzymatic oxidation. The great majority of radiochemical reactions are apparently irreversible *in vitro*. If a radiation reaction similar to the last one described were to take place *in vivo*, natural enzymatic processes could restore the *substrate* to its natural state, and the acetaldehyde formed could be reduced again to ethanol.

Present status of the "target" theory

51. According to its original meaning given by Crowther in 1924, a "target" in radiobiology is a sensitive cellular structure whose inactivation by one or several ionizations (hits) would result in the observed biological effects.[131] When ionization takes place exclusively in the sensitive structure (direct effects) the dosage to effect relationship has enabled one to calculate a target volume. In the case of dry or highly protected small viruses which are inactivated by a single efficient ionization, it has been possible on this basis to measure their volume and molecular weight and obtain values in agreement with those obtained by other methods. As water is a major cell constituent, it can be expected that part of the biological effect of radiations is of an indirect nature: this raises new problems as to the applicability of the target hypothesis to living cells. If all indirect effects could be suppressed, as it is thought they are in dried seeds, there would be no problem. At present there is no certain way of doing this: loading the organism with chemical protectors, freezing the cells or reducing the oxygen tension may not do it efficiently because it cannot be foreseen to what extent a chemical protector will reach the cellular structure under consideration, and because free radicals may remain frozen at or near their site of origin until the cells are thawed for biological assay. Therefore, more knowledge is needed about the relative importance of indirect effects and about the distances over which free radicals may diffuse before being neutralized or before reaching the cellular targets. In order to have a clear-cut criterion which can be observed, the biochemical or biological reactions controlled by the targets should be well defined. Probably, when these conditions are satisfied, it will be possible to use the target concept as a useful analytical tool. Work in this direction is in progress.

III. Biochemical Effects

52. The *sequence of chemical events* from the moment when the cell constituents are subjected to radiation up to the time the biological effects become apparent can conceivably be discovered with biochemical techniques. The search for an immediate or initial biochemical event will thus be the first step in this attempt. Two approaches have been used by studying the effects on cellular constituents and on biochemical mechanisms.

Cellular constituents

53. The search for structural damage to important cellular constituents can be done by assaying, as soon as possible after irradiation, the biological or the physicochemical properties of various cell components of which the integrity appears to be important for the economy of the cell. Enzymes or nucleic acids can be examined in this way, but although high doses have been used no definite clues have so far been reached, despite the very great number of observations. The general conclusion seems to point to the apparent radioresistance of the majority of

cellular proteins; and even sulfhydryl groups, which are very radiosensitive in dilute solution,[132,134] do not appear to be considerably damaged *in vivo*.[126,133] Similarly, essential coenzymes and vitamins do not seem significantly altered immediately after irradiation.[126] This is due to the fact that only a very small percentage of the constituents are affected unless very high dosages are applied.[126]

54. It must be realized that in such attempts to identify radiosensitive molecular species by looking for the oxidation of SH groups or changes in molecular asymmetry these molecules are usually considered in bulk, and even when specific analysis is undertaken, it is often found, as is the case of coenzyme A, that no alteration can be detected.[135] These negative findings do not exclude the possibility that a small number of molecules of a type controlling key mechanisms (cell division for example) or having a particular location may still be altered —but at present, general knowledge about the existence of such specific molecules is lacking.

55. In the case of genetic constituents (desoxyribonucleoproteins), which presumably constitute a class of relatively few molecules each having a very high degree of biological specificity, the alteration of a single unit would result in some cellular damage which would become expressed at the end of the chain of reactions it initiated.

56. The question of the radiosensitivity of nucleic acids *in vivo* seems still to be controversial, although evidence indicates that *nucleoprotein* complexes are probably dissociated in many tissues as a result of moderate irradiation.[67,126] It has been calculated, on the basis of *in vitro* measurements, that a dosage of 100 r could damage 100 to 200 molecules of DNA in a mammalian cell,[137] and this figure does not disagree with the data indicating the stability of pneumococcus DNA when irradiated *in vivo*[136], the dosages used in these experiments not being sufficient to cause any significant inactivation.[69] Thus, a very much lower dosage than 1 r would be theoretically sufficient to alter permanently some genetic constituent in a single cell. In this case, not all cells would have one of their DNA molecules affected. However, nothing is known on the possible interactions that intact cells could have on the affected ones, either by influencing their recovery processes or by competing effectively with them (selection). Knowledge on the behaviour of an affected cell in a normal population would be of great interest to understand low dosage effects.

57. There is no reason to believe that ribonucleoproteins are not as radiosensitive as the desoxyribonucleoproteins, but very little is known about the number of units of each type which a cell is likely to possess and even less of the specific reactions they control. Chromosomal ribonucleoproteins could very well be concerned with the duplication of genetic material in dividing cells, as suggested by recent work on bacteriophage synthesis.[138,139,140]

58. Still less information is available concerning the possibility of other cellular constituents playing key roles; many remain to be discovered and further fundamental research is required.

Biochemical mechanisms

Energy-forming systems

59. More information is available from the study of integrated biochemical reaction chains, like those of *glycolysis* and *respiration*, when studied at various times after irradiation. These systems result in the building up of compounds rich in chemical energy which can be used for biosynthetic reactions and cellular work. In radiosensitive organs like bone marrow, spleen and thymus, such reactions as aerobic phosphorylations seem already to be impaired thirty minutes after irradiation by 50 r (effects on mitochondria), but it cannot yet be stated whether these radiobiological processes are the cause or the result of other biochemical damage.[141,142]

Synthetic mechanisms

60. In dividing tissues, the most constant finding is an inhibition of the synthesis of desoxyribonucleic acid.[131,143,144,145] In micro-organisms like yeasts, the homogenity of the population makes experiments more easily interpretable; and it has been found that this inhibition is only temporary and that synthesis resumes after various lengths of time.[144] In other instances, there may be a short time-lag before this inhibition occurs. However, the mechanism of DNA synthesis, although beginning to be experimentally approached, is not understood. As has already been pointed out, it may be dependent even in normal cells on protein or ribonucleic acid metabolism; and in bacteriophage it is probably dependent on such metabolism by the host cell. The nature of the initial step of radiation damage remains to be determined. On the basis of bacteriophage inactivation, it has been suggested that the DNA model, or template, on which the new molecules are thought to be formed, has been altered in such a way as to make its reduplication impossible. The temporary inhibition of DNA synthesis may lead to abnormal DNA formation and this is perhaps related to the killing of cells and to mutation, but in what exact manner is not known.

61. So far, the syntheses of ribonucleic acid and proteins and lipids in bulk do not appear to be consistently impaired by radiation and may even be enhanced, but these compounds are very complex and their study in bulk form, the manner in which it has mostly been carried out so far, cannot be regarded as adequate. Proteins and RNA, bound to the chromosomes and other nuclear and cytoplasmic structures, are probably very complex and each fraction should be studied independently.[144] This will only become possible, however, when more is known about the chemical composition of cellular structures and when refined analytical procedures are available.

62. The inhibition of *induced protein synthesis* in micro-organisms has usually been found to be resistant to radiations, except in the case of hydrogenlyase in E. Coli.[146] In mammals, a few cases of induced synthesis of enzymes are known: the tryptophane peroxidase activity of rat liver can be increased if the animal is injected with large amounts of tryptophane. This process is inhibited by radiations, but this inhibition only becomes apparent after two or three days.[150] However, if tryptophane is *not* given to the animal, an *increased* activity of the peroxidase during the first few hours after irradiation can be observed, but this increase does not occur in adrenalectomised rats and is therefore due to a secondary adrenal stimulation.[151,152] There are therefore two conflicting mechanisms which have opposed effects. It has furthermore been shown that the occurrence of infection in irradiated mammals can be related to an impaired synthesis of *antibodies* if irradiation takes place before the injection of the antigen;[146,147,148,149] this is not necessarily due to the depletion of antibody-forming cells, but

might be related to the inhibition of the *induced synthesis* of a specific protein, a complex process generally considered to be related to the metabolism of ribonucleic acid, but which is not understood. The complete process of immunological response (the sequence of events between the invasion of the organism by an antigen and the synthesis of a new specified antibody) is also not properly understood and the cells which are concerned are just beginning to be identified. The process of induced synthesis is believed to be related to ribonucleic acid metabolism, and in micro-organisms it is quite sensitive to U.V. light absorbed by their constituents which affects the synthesis not only of the new proteins but also of ribonucleic acid.[153]

Effects on transport mechanisms in the cell membrane

63. Enzymatic systems at the surface of the cell membrane take a prominent part in the active transport of metabolites through the cell membrane,[154] but, although cell permeability has often been said to be affected after irradiation,[155,156] few critical experiments have been performed. It has been shown, for instance, that lethal irradiations and still higher dosages have often led to a leak of potassium ions into the medium; this has been proved in erythrocytes, in muscle but not in liver.[157] Similar phenomena, if existing in nerve cells, could be a basis for explaining some of the nervous symptoms of irradiation. Surface mechanisms can be affected in yeasts by U.V. light 365 mμ. without apparently producing other effects than delaying mitosis; these surface lesions cause considerable loss in potassium.[158]

64. The loss of small organic molecules like adenosine triphosphate has been shown to occur from irradiated micro-organisms,[159] and techniques of tissue culture will make it possible to establish whether such behaviour applies also to mammalian cells. In mammals, it is known that amino acids and other small molecules (taurine for instance) are released in the blood stream and urine,[160,161] and this might be the result of impaired permeability.

65. The exact significance of these various biochemical effects is difficult to discuss because our present knowledge of the sequence of biochemical mechanisms taking place in a normal cell and their interrelationship is still very fragmentary.

IV. Cytological effects

66. In order to explain the biological effects of radiation, cytologists have tried for the last half century to identify abnormal cell structures.

Nucleus

67. *In the cell nucleus*, the most conspicuous damage is in the *chromosomes*, which are very sensitive and frequently grossly altered; irradiation as low as 25 r or even less is sufficient to induce chromosome aberrations in embryonic nerve cells[162] or in many plant tissues.[163,164]

68. Irradiation causes the breakage of chromosomes, which probably occurs during exposure; this is followed by normal or abnormal recombination of the broken ends; but these may remain separate. As not only the molecular integrity but also the order of the genes on the chromosomes is important, this damage may lead to genetical effects simulating mutations. Point mutations are molecular alterations of genes usually not accompanied by visible aberrations, and they may perhaps concern only a very few sub-units (nucleotides) of genetical material;[165,166] however, a point mutation could occur at the point of breakage and reunion of the chromosome and in this case the damage would be visible. Two types of mechanisms for chromosomes breakage appear to be possible;[35] the first would be the result of the breaking of weak ionic bonds, the second the rupture of stronger covalent bonds. In the first case, restitution is possible in the absence of external energy sources; in the second, energy of respiratory origin is necessary. This interpretation is by no way definitive; it is the one which best fits the present experimental data, but its simplicity is obviously a reflection of our ignorance of the over-all molecular structure of chromosomes and of the dynamic mechanisms of chromosome function. It is presumed that ionization must take place in the gene itself or in its immediate vicinity to cause a mutation.

69. Less defined damage, making the chromosomes stick to each other, is also observed; the result of this stickiness is, as is often also the case for well-defined abberations, an uneven distribution of chromosomes between the daughter cells, which affects the process of mitosis or the survival of the cells.[162,167] Staining abnormalities of the nucleus have frequently been observed.[70,168]

70. New techniques have only recently been developed for mammals, making possible in them the identification of all the chromosomes in a sufficient number of cells for the quantitative study of aberrations, which would lead to the establishment of dose effect relationships in men. Observations of this kind will be extremely laborious and one cannot expect much information before many competent observers have been trained.

71. The morphology as well as the number of *nucleoli* (small nuclear spherules characterized by their high content of ribonucleic acid) may be altered in mammalian cells.[169] The total cellular volume may increase as a result of irradiation, as the volume of the nucleus often does; the nucleoli may become swollen, fragmented or vacuolated.[167,170] The precise function of the nucleoli in normal cells is far from completely known, but it may be related to such diverse processes as cell differentiation, protein synthesis and coenzyme synthesis, and their obvious relationship with the chromosomes in many instances make these organelles of prominent interest for the proper functioning of the cell.[171]

Cytoplasm

72. Nuclear swelling is often accompanied by cytoplasmic swelling, and giant cells are often observed after irradiation of micro-organisms as well as of mammalian cells.[172] The fact that the dry weight or total nitrogen increases at the same time indicates that many synthetic reactions have not been interrupted. Swelling of cells (or elongation of bacteria) appears to be the result of an impaired cytoplasmic cleavage.[173,174,175,176,179] This cellular swelling has often been the basis of a misinterpretation: many references to the *stimulation of growth* of irradiated organisms can be cited. Actually, as in the case of seedlings, this is merely the result of the elongation of non-dividing cells:[176,177,178] the inhibition of one process (cell division) may result in the increase of available energy or building blocks for other reactions, thus merely shifting one steady state to another. The energy of radiation and its random distribution is such that the chances of obtaining deleterious reactions appear greater than those for specifically removing inhibitory processes, another logical mechanism by which stimulation could be explained. Effects of radiation should always be thoroughly analysed before they can be assumed to be useful to the irradiated subject.

73. The cell cytoplasm is known to contain a variety of particular structures, the exact identity of which has not yet thoroughly been worked out.[180]

74. *Mitochondria* are the largest of cellular particles; they contain most of the enzymes and coenzymes responsible for cellular respiration which release the major part of energy used in biochemical reactions; they also have important functions in lipid metabolism.[192] They have been observed to swell or show abnormal staining in irradiated spleen cells,[181,182,183] a finding which has been supported by biochemical evidence (inhibition of oxidative phosphorylation).[184,185] If, after irradiation, the behaviour of the various biochemical functions which are attributed to mitochondria were compared, it should be possible to draw a consistent picture of their alterations;[185] unfortunately the experiments have seldom been carried out in comparable conditions.

75. The following have been described:

(*a*) An inhibition of respiration and phosphorylations chiefly in thymus and spleen; the phosphorylation processes appear to be more sensitive than respiration.[184,186,187]

(*b*) An increase of spleen adenosine-triphosphatase which seems to be independent, at least initially, of the inhibition of phosphorylation.[186]

(*c*) An altered lipid metabolism characterized chiefly by an increased synthesis of the phospholipids of the liver;[188] however in spleen and thymus it is slightly lower or remains normal. It must be emphasized, however, that lipid synthesis may not necessarily be linked to mitochondrial integrity, as suggested by a number of experiments.[189,190,191]

76. Thus, the different reactions to radiation of three different mitochondrial functions do not appear to respond identically. This raises the problem of the identity of the mitochondria performing all these three functions. Much better controlled work, where several properties of the same particles are investigated in identical conditions, could help to solve this important problem, and radiations could perhaps in this instance be useful as an analytical tool: the site of lipid metabolism could be a radioresistant type of mitochondrion.

77. It must finally be kept in mind that respiratory processes appear, as in yeast, to be controlled by nuclear or cytoplasmic factors;[193] the latter may or may not be identical with the cytoplasmic particles carrying the respiratory enzymes themselves. An alteration of these controlling mechanisms could very well be the origin of late radiation effects on these functions.

78. *Microsomes* form another class of smaller, cytoplasmic structures organized in a reticulum, as seen by the electron microscope.[194,195] They have a strong affinity for basic dyes, a condition which is strikingly augmented in tissues undergoing differentiation and actively synthesizing protein; in the course of these processes, ribonucleic acid, chemically related to the desoxyribonucleic acids constituting the nuclear genes, undoubtedly plays an important part. There does appear to be a functional relationship between microsomes and nucleoli, but its nature is not understood. These particles are at present considered to be the major site of protein synthesis.[171]

79. Surprisingly, electron microscopy has not been much used for the study of the structure of the irradiated cytoplasmic reticulum and the scanty observations so far performed in the thyroid and in the testes have not revealed any damage to this reticulum.[196]

80. If the microsomes are considered from a dynamic point of view and the cellular functions to which they are related are studied, several conclusions can be tentatively reached.

81. In general, *protein synthesis* does not appear to be impaired immediately after irradiation,[198] and it is, on the contrary, often enhanced: however, this increased activity is often followed by a depression, as in the case of the synthesis of the protein moiety of hemoglobin.[197,199] This bimodal response to radiation, often found for protein synthesis, makes it difficult to interpret the variations of the serum proteins[200] in irradiated animals where a very complex picture is often obtained and when the many results available are difficult to compare on account of different methods and timing of the experiments.

82. The inhibition of the *induced synthesis* of tryptophane oxidase and antibodies are perhaps also related to microsome activity.[150]

83. *Cholesterol synthesis* is also related to the integrity of microsomes[201] and is often enhanced after irradiation; when it is inhibited as in spleen, this only becomes apparent after twenty-four hours.[97]

84. In most cases, the effects of radiation on microsome function probably do not become expressed immediately after irradiation. It will not be possible to understand these late effects until the fundamental facts about protein synthesis and their relation to nuclear activity are known. Experiments on enucleated unicellular organisms have shown that the nucleus has a definite but remote control over the cytoplasmic ribonucleoproteins;[171] the irradiation of non-nucleated cytoplasm in the amoeba has shown that at least ultra-violet light affects cytoplasmic ribonucleoproteins quite rapidly.[202]

85. *Lysosomes* form a type of cellular particle chiefly studied in liver; they are intermediate in size between microsomes and mitochondria;[180] they are characterized by a high content of iron and by their association with several enzymes like desoxyribonuclease II, ribonuclease, cathespin, glucuronidase, and acid phosphatase. As the activity of the first three of these enzymes has been found to increase in tissue homogenates or in the blood stream after irradiation,[203,204,205,206,207] it could be suggested that this is a result of damage to the lysosomes; critical experiments in which enzymes are assayed simultaneously in an irradiated animal might prove this hypothesis. In the case of cathepsin, the increased activity can be related to the disappearance after irradiation of an enzyme inhibitor normally present in the blood.[207,208]

86. *Chloroplasts*,[209,212] the chlorophyl-containing cytoplasmic particles of plant cells, and *kinetosomes*,[210] the particles related to flagella in protozoa, are both endowed with genetic continuity: this gives to these structures great theoretical importance. If the speed of multiplication of these structures can be reduced to a greater extent than that of cell division, one can expect to find that some of the daughter cells have completely lost them. The reverse could also be true, and recent work on moderately irradiated grasshopper testes[196] has shown in the electron microscope the appearance of supernumerary tail filaments and centrosomes, probably related to the kinetosomes of protozoa. These observations have led their authors to an interesting theory of radiation damage based on the synergistic action of non-specific molecular displacements leading to the formation of abnormal

structures.[196] Extensive work on irradiated plant cells has led to the demonstration that the activity of several enzymes bound to the chloroplasts were altered.[211]

V. Biological effects

87. The effects on homogeneous populations of cells will be considered first, and then those on complex organisms.

Homogeneous cell populations

88. Cell populations such as micro-organisms, protozoa, unicellular algae, cultures and surviving suspensions of cells from multicellular organisms like fibroblasts, bone marrow cells, gametes and certain cancerous cells have been extensively studied.[1,213,214,215,217,218] Recent techniques make possible the culture in liquid media of almost any type of mammalian cell;[177,178] these cells are capable, *in vitro*, of forming organized structures recalling the original tissue they come from,[216] which should be of great value in studying problems of cellular organizations and in understanding multicellular organisms. These cell populations have been irradiated in rather comparable conditions, and they have been shown to react in very similar ways.

89. When *fundamental properties* of the cells such as survival, *cell multiplication* or mitosis, *increase in dry weight, differentiation* of non-mature cell types, cell *movements*, or *permeability* of the cell membranes are studied, one can usually describe a *common pattern of reaction to radiation.*

90. On the other hand, cells performing *specialized functions* may react to radiation in a specific manner related to this function. In *multicellular* organisms, important *interactions between the different tissues* have also to be considered.

Mitosis (i.e., cell division)

91. Cells are rarely killed immediately, but usually die after having attempted division or after having undergone one or several divisions. Mitosis itself is interfered with and is usually *delayed*, if irradiation happens early enough in the mitotic cycle. This has been examined most elegantly by direct observation on hanging drop preparations of neuroblasts from grasshopper embryos.[167] These experiments have shown the existence of a very critical stage of cell division during the period when the chromosomes condense as visible threads and when both the nuclear membrane and nucleolus disappear. Irradiation *before* this critical stage usually makes the whole process stop for a duration depending on dosage; *after* it has passed this stage, the mitotic events do not appear to be interfered with if dosages are small. It is remarkable that, if applied at the right moment before the critical period, dosages as small as 8 or 16 rad will delay the progression of mitosis in this type of cell. These observations are essentially similar to the previous analyses on fibroblast cultures;[220,221] they also fit rather well with the experiments on irradiated gametes of the sea-urchins, where cleavage of the fertilized embryos obtained by the conjugation of irradiated gametes (either or both of which have been irradiated) is also delayed, if irradiation occurs before early prophase in this case.[222] If irradiation occurs afterwards, it is the subsequent cleavage which is slowed down. This general picture of mitotic delay may be subject to some alteration when different types of cells are considered; less direct methods of observation may have led to a different timing of the critical period in other cells.[219,221] Also, in each cell type, although the general course of mitosis is quite similar, the duration of each phase and sometimes the exact denomination of the stage considered may vary to a considerable extent, which makes exact comparisons very difficult.

92. The exact cause of the inhibition of mitotic division is not known. It has been suggested that it is related to the inhibition of DNA synthesis[214,223] which occurs frequently — but some instances where cell division is inihibited with apparently normal DNA metabolism will force us to reconsider this view.[224] DNA synthesis, as stated previously, is a complex process; it is perhaps associated with chromosomal protein[225] or RNA synthesis,[138] of which next to nothing is known. It has been suggested on the other hand that an interference of radiation with the oxido-reduction of sulfhydryl compounds known to occur during cell divisions[228,229,230] might also be one cause of its inhibition; inhibition of mechanisms of cytoplasmic cleavage[226] or of spindle formation[227] are other plausible hypotheses.

Mutations

93. It has been stated earlier that cells which do not die after several divisions are said to recover. This statement is very imprecise, because all that is known is that these cells *look* as if they had recovered. However, in certain instances although they continue to have a quite normal appearance, they have undergone *mutation.* These changes have been observed most clearly in bacteria, moulds, and other unicellular autotrophic or heterotrophic organisms; and very recently, the studies of cultures of isolated mammalian cells have suggested that such mutant forms also exist amongst the survivors.[231] These mutations are characterized by the fact that the surviving cell as well as *most of its descendants* have been affected in a way which makes them *permanently* incapable of performing some biochemical reaction. If this biochemical reaction (for instance, the formation of an essential building block) is necessary for the cell to grow and multiply, the mutation will lead to the arrest of growth and multiplication, and finally the cells will die, if this essential building block is not provided in the culture medium. It is believed that *there is a period of time following irradiation during which the process of mutation is not fully established.*[232,233,234,235] What takes place during this time is not known—but it is possible, at least in the case of ultra-violet irradiation of micro-organisms, that the expression of damage depends on the synthesis of some protein. Although this time-lag gives the possibility of interfering with mutagenesis[234,236]—a subject which will be discussed more thoroughly in another section—it is generally accepted that this damage *once fully established cannot be reversed by non-genetical processes.* In addition to induced mutants there are always a certain number of *spontaneous* ones, which arise in the absence of any added external agents.

94. *Back mutation* (reverse mutation), the apparent reversal of the previous mutation and the evolution from dependency to independence of some specific metabolite, may occur spontaneously or by irradiation of the mutant; apparently there is what could be called a true recovery of the cell or at least of that part of the cell which had first been altered.[237] However, the spontaneous phenomenon has a small probability of occurring and the process of back mutation, *unless it could be directed*, is not a practical recovery process.

95. Other mutagenic agents (lower energy radiation like ultra-violet light,[238] many toxic compounds and chemical analogues to normal building blocks)[239,240] are all useful in helping to clarify the mechanism of mutations. Chemical analogues, for instance, compete with normal building blocks and may often replace them in important macromolecules like nucleic acids, sometimes preventing their reduplication or their normal functioning. Comparison of ultra-violet lights of different wavelengths will indicate which of them is most effective and enables the nature of the chemical groups absorbing the energy to be determined. The use of these agents is of very great importance in elucidating the mechanism, not only of mutation, but also of chromosome breakage and of mitosis, which they are capable of disturbing.[239]

96. Genes presumably control the biochemical mechanisms (many of which are located in the cytoplasm) responsible for producing enzymes or other specific cellular constituents.[241] It is possible to imagine that, as a result of irradiation, the block in the reaction chain between gene and enzyme-forming system could occur in some intermediate *cytoplasmic* structure. If this structure is one which, like the chromosomes and the genes they carry, has to reproduce itself at each mitosis in order that each daughter cell be identical to its parents, and if damage has rendered the reduplication of the original structure impossible, one will obtain a *cytoplasmic mutation*. Nothing much is known about these, but the induction in yeasts of respiratory deficient strains by poisons or radiation and the demonstration that this deficiency is not necessarily of nuclear origin, indicates the existence of heritable cytoplasmic characters.[193,242]

Movement

97. *Cell mobility* can be stopped by irradiation, but usually very high dosages are needed for such an effect. Irradiation of spermatozoa[244] may result in the loss of motion, probably as a consequence of the inhibition of phosphorylation;[243] this causes them to become infertile, but the dosages are much larger than the ones required to delay cleavage of the fertilized egg. Nothing specific is known of the effects of radiation on the cellular migrations which occur in the developing embryo. On the other hand, radiation is known to inhibit phagocytosis in mammalian polymorphonuclear white blood cells,[245] but phagocytosis is a complex phenomenon and this effect is not necessarily due to the inhibition of movements. Alterations of cytoplasmic or nuclear movements inside living cells might also give useful indications, but so far their quantitative measurement is difficult.

Membrane phenomena and ionic equilibria

98. The statement frequently made that radiation alters the cell permeability needs to be specified. The exchange of inorganic or organic molecules and ions between cells and their natural environment is a very complex process, because many substances have to be concentrated inside the cell against a concentration gradient, a process which requires energy,[154] and inhibition of permeability could result from the inhibition of energy-forming systems. This is the case for K^+ or carbohydrates; in the case of the latter, complex enzymatic systems, located on the cellular membrane, have been described, and it would furthermore not be surprising that this organized structure be upset by radiation as are other patterns of cellular organization.

99. It has been shown in many cases that potassium leaks out of many irradiated cells like erythrocytes,[246,247,248] and cardiac muscle,[250] but not out of liver or kidney,[251] or striated muscle.[249]

100. The entry of glucose or amino acids into cells is also dependent on surface enzymes, and it should be clarified whether an inhibition of these systems might affect secondarily synthetic or energy-forming mechanisms. In micro-organisms (*E.Coli*, yeasts), it is known that the induced synthesis of many enzymes is not inhibited by X-rays[252] for doses which completely arrest cell multiplication, which indicates that the inductor substrates are still capable of penetrating into the cells. However, quantitative studies have not been performed. On the other hand, it has been proved that in similar organisms (*E.Coli*) irradiation leads to the diffusion of many nucleotides[159] into the outside medium, as well as of potassium, which has already been discussed (paragraph 63).

101. In mammals, it has been found that when glucose is injected under the skin immediately after irradiation, its entrance into the blood stream is slowed down.[253] The passage of metabolites from the hypodermal region into the blood capillaries could be a more complex phenomenon, because it involves the passing of the molecule through an organized tissue. The same applies to the inhibition of the intestinal absorption of glucose, which is diminished three to six days after total body irradiation in rats. However, in this case the inhibition is accompanied by important cytological damage.[254] The case of the barrier separating the eye from the blood stream[255] as well as many others[156] have also been studied with similar results.

Cell death

102. Irradiated cells die either immediately (i.e., during irradiation) or after a certain delay: in the former case, much higher dosages are needed, and death can be attributed to a general denaturation of cellular constituents. Many conflicting results on cell death have appeared in the literature; this can be accounted for by the difficulty in defining cell death: in micro-organisms, for instance, death has been defined as the inability to form visible colonies on agar plates. Furthermore, the primary cause of cellular death may differ from one system to another, and it is not necessarily unique; any of the cytochemical, biochemical, physiological or genetical effects of radiation so far discussed could each take part in killing the cell. A mutation in a micro-organism leading to the inability to form an essential building block will be "lethal" *only* in the case where the culture medium does not contain this substance.

103. Delayed death of dividing cells occurs after one or several cellular divisions have taken place,[220,256,257] and it may often be linked to chromosome damage,[258] but it could also be due to nutritional or other deficiencies, such as occur in a non-dividing population. Delayed death is caused by much more specific damage than immediate death, and its study is thus of far greater interest. The doses required for obtaining delayed death may be different not only for cells of different species,[1] but also for closely related cells such as different strains of the same bacterial species.[259]

104. Recent experiments on *cultures* originating from different single mammalian cells have shown a very similar sensitivity;[231] this probably results from the fact that in these abnormal conditions cells undergo relatively

rapid division, whereas in the whole organism this process may be extremely slow and may differ from one tissue to another. When penetrating radiations are used, it can be assumed that each cell of an irradiated population receives the same amount of radiation. In an average-sized mammalian cell, submitted to an irradiation of 1 r, several hundreds of ionizations occur, and the probability of a structure being damaged will depend on several factors, including its size and the radiosensitivity of its constituent molecules *in vivo*. It has been calculated that 100 r to a mammalian cell nucleus produce 100-200 hits into the DNA; 1,000 r to a bacterium will produce of the order of 5 to 20 direct hits in the DNA alone, and every radical which might reach the DNA could damage another molecule.[69] Alterations of DNA could be one cause of late cellular death, but other cellular constituents are also damaged. It can be shown that some cells die while others recover and apparently behave again like normal ones. This probably results from differences in the distribution of the energy to "critical" and to less "critical" molecules and it has to be remembered that it is the remaining physiological activity of each cell constituent which will determine the final biological effect.

Effects on viruses and K particles in Paramecia

105. Radiation effects on such specialized biological systems may at first appear to be out of place in a general survey as this one, aiming at understanding radiation hazards to man. However, these systems are very closely related to chromosomes (and presumably the genes they carry) and to many cytoplasmic particles; they consist of nucleoprotein, and the mechanism by which viruses reproduce autocatalytically offers the best model at present available for the study of the reduplication of cellular nucleoproteins. Viruses are very important in radiobiology, because they can be studied both as chemical entities *in vitro* and they can be irradiated independently of the cells they multiply in. Bacterial viruses (bacteriophage),[260,261] some of the animal viruses and the cytoplasmic K particle of *Paramecia*[262] are desoxyribonucleoproteins, like the bulk of the chromosomes; plant viruses and some animal viruses are ribonucleoproteins, others are desoxyribonucleoproteins.

106. Bacterial viruses are the ones most attention has been paid to, and the following fundamental facts have been discovered and have in some cases been confirmed using other viruses.

107. Ionizing or ultraviolet radiation applied *in vivo* or *in vitro inactivates them, i.e. interferes with the possibility of their being self-duplicated inside the cell.*[260,261,262]

108. For certain strains, non-irradiated bacteriophages are capable of growing in bacteria heavily irradiated by X-rays or ultraviolet radiation, indicating very clearly that *the self-duplicating structure itself* has to be affected and that the bacteria remain capable of supporting phage multiplication.[263,264]

109. If the conditions of infection are such that there are *several* ultraviolet inactivated bacteriophage per cell, for certain strains of bacteriophage, the intact parts of each virus can *recombine* into a complete new unit, which is again capable of duplication (this is called *multiplicity reactivation*).[265] This is a crude and probably quite inaccurate way of explaining a complex mechanism of which little is known. This type of reactivation has also been described for X-rays.[266]

110. Experiments like these may have very general implications for the understanding of damage and of recovery processes taking place in cells of more complex organisms and therefore should be vigorously encouraged.

Effects on lysogenic cells

111. Certain types of bacteriophages invade their host but do not multiply in the usual way; on the contrary, they appear to become integrated into the bacterial desoxyribonucleoprotein and thus reduplicate simultaneously with the bacterial nuclear material without causing any apparent trouble to the cell. However, extremely low dosages of irradiation as well as a variety of other agents induce the transformation of this "prophage" to a virulent bacteriophage, which will multiply and finally lyse the infected cell.[267] In certain strains of lysogenic bacteria, a dosage of 0.1 r may give a measurable induction, and the linearity of the dose-response curve for this "genetic" effect has been demonstrated down to such low dosages.[37,106] What characterizes induction is that it takes place in almost 100 per cent of lysogenic cells, whereas mutation only takes place in a small number.

112. Experiments on infected micro-organisms have also shown that a virus is capable of becoming integrated into the genetic material of the host and of *transducing* some genetic characters from one genetic type of host to another.[166,268] It is not unlikely that processes similar to bacterial transformation by DNA or to transduction involving the transfer of genetic material from one type of cell to another, also exist in mammals. If such phenomena were discovered, *directed reversed mutations might become possible in mammals.*

Differentiating cell populations

Embryonic development

113. Gametes arise from the differentiation of stem cells, the oogonia or spermatogonia, which takes place in the gonads. This differentiation (oogenesis or spermatogenesis) is a process during which the double genetic equipment (*diploid*) existing in the stem cells as well as in the somatic cells is halved evenly through the complex process of *meiosis* to give daughter cells, which will produce gametes containing only one gene of each kind (*haploid*). Fertilization will result in the fusion of the parent nuclei, and the usual diploid number of the somatic cells is thus obtained.

Irradiation of gametes

114. We have seen that when either of the gametes is irradiated, the first cleavage of the fertilized egg is delayed; if the embryo is then left to develop, the cleavage divisions usually proceed apparently quite normally up to the blastula stage. However, embryonic development usually comes to a permanent stop before the completion of blastulation or during early gastrulation; this is one of the numerous examples of delayed death.[269] The fundamental biological situation is that gastrulation is the first stage of development during which *cellular differentiation* occurs: this process is preceded by a striking increase in the metabolism of ribonucleic acid (both in the cytoplasm and nucleolus), as is the case in most biological processes where intense protein synthesis and differentiation is taking place.[270] Furthermore, during gastrulation important cellular movements lead to the formation of three different cellular layers which ultimately become organized in tissues

and organs. Some of the cells in certain layers are capable of *inducing* specific differentiation processes in others. There is not just a change in the "geographical" relationship of the cells as a result of these movements, but their apparent uniformity up to the stage of the blastula is lost; this is demonstrated by the fact that the *nuclei* lose the general potentialities they had until then.[271]

115. The cause of the death of embryos obtained from oocytes fertilized with irradiated sperm appears certainly to be related to *nuclear damage:* the sperm cell contains only very little cytoplasm, and the damage can remain hidden, as it may do in mutations, over many cellular generations. Cell divisions appear to be blocked as a result of incomplete fusion of the maternal chromosomes with the abnormal ones of male origin, a situation leading eventually to abnormality and uneven distribution of chromosomes between daughter cells.[269,272,273,274,275] It is important to notice that the process of cell division becomes inhibited at a stage of development where the genetic material is presumed to initiate differentiation. If, however, the fusion of the abnormal paternal chromosomes with the normal maternal ones is completely prevented (which can be done by using *higher* dosages of radiation), a situation arises where the abnormal nucleus is eliminated, and in this case an *apparently normal* embryo will develop if the species studied are capable of parthenogenetic development.[269,272,275] This is one example, amongst others, where dosage-effect relationships appear to be non-linear and even paradoxical; *higher* dosage producing *less* final damage than lower ones. The explanation is that complex mechanisms of development, secondary to the initial damage to the chromatin are observed: this damage, however, is probably related in a simple way to the amount of irradiation received. A similar paradoxical situation may be found in the experimental inductions in the embryo of certain abnormalities such as microphthalmia[273] and this can be logically explained by the existence of some competition with other lesions at higher dosage.

116. In the wasp *Habrobracon*[276] and in silk worm[277] the reverse situation is possible, and the fusion of a normal sperm cell with a highly irradiated egg cell may lead to an androgenic embryo (containing only its *father's* chromatin). Experiments such as this point again to the very important role of radiation damage to the cell nucleus. Nuclear damage (genetic) is probably also responsible for the various forms of abortion or of malformations of offspring born of parents, one or both of which have been irradiated. In this case, the development of the embryo ceases at some stage of organogenesis, sometimes even after birth. However, as different *stages of gametogenesis* have different radiosensitivities, one expects to have a different probability of abnormal offspring when mating occurs at different times after irradiation.[273] The longer the time lapse before conception, the smaller the probability of abnormal development, because it has been found that the earlier stages are the least sensitive ones, at least in mice.[25,278] With slight irradiation, development may in many cases proceed and this will result in more or less dramatic expressions of genetic damage visible in the offspring.

Irradiation after fertilization

117. If irradiation is given at different *stages of embryonic development*, the inhibition of cell division and differentiation and cell death may cause the development to be either completely or partially stopped. In the mouse, the pattern of response to irradiation (200 r) of the embryo is the following: irradiation of the mother after fertilization but during the pre-implantation period leads to a high incidence of prenatal death; however, the survivors have very few major abnormalities; this means that only the slightly affected embryos survive. In contrast, if irradiation occurs after the embryo is implanted in utero, during the period of organogenesis, death usually occurs only after birth—but it is much less frequent; on the other hand, there is a very marked increase of malformations of the embryo. During early embryonic development (if irradiation takes place during the formation of the neural folds), malformations may occur in the eyes, brain and medulla but also in the kidney and liver. Irradiation at a slightly later stage of organogenesis gives rise chiefly to abnormalities of the skeleton of various types. There appear to be short critical periods of development during which certain types of abnormalities arise with very great frequency.[279]

118. The exact mechanism of all these effects, which are all possible in humans, is far from being well understood on account of our ignorance of many important facts concerning embryonic development, such as the nature of *induction* (interaction between neighbouring tissues), the cause of *morphogenetic movements* or the nature of *genetic expression*, that is, the mechanism by which one single cell is capable of becoming differentiated into a multitude of daughter cells performing a variety of functions.

Dosage-effect relationships

119. These have been studied in certain cases, and for most bone abnormalities they have been found to be of the *sigmoid type.*[280] In the case of the decreased weight of the foetus at birth, the dosage relationship is *linear,*[280] and litter size appears to fall off logarithmically with dosage to the gametes.[281] A constant finding is that a higher dose not only increases the incidence but also the degree of malformation and the length of the sensitive period during which a specific response can be induced.[280] It has been shown that a dose as small as 25 r to the mouse embryo has led to the induction of minor but nevertheless well defined abnormalities. It is difficult at present to know how such small doses could affect human embryos, but it can be expected that very minute malformations of the brain, which could perhaps not be detected in experimental animals, will result in some kind of psychological disorders. Responses to lower dosages still could probably be detected if a greater number of animals and more refined tests were used. The case of leukemia, also believed to be inducible by irradiation of the human embryo,[282] is discussed in detail in chapter V and annex G.

Adult organisms

Differentiation

120. Some undifferentiated cells are carried on into the adult organisms and these stem cells go on differentiating throughout life: the white blood cells are formed in the bone marrow and in the lymphatic tissues (lymph nodes and spleen and other organs). The lymphatic tissues are considered to be of major importance in antibody formation. The red blood cells originate from bone marrow and during embryonic life from spleen and liver. In rodents, myelopoesis and erythropoiesis continue in spleen during adult life, but not in man. This is one of many physiological differences it is essential not to overlook when one transposes the results from experimental animals to man.

121. Adult organisms contain other tissues *continuously regenerating* from stem cells, such as epithelia (skin, gut, etc.) or bone; finally there are tissues in which *few cell divisions* take place (liver, kidneys, pancreas, brain, or conjunctive tissue).

122. As in the case of isolated cells, experimental evidence points to the *particular radiosensitivity not only of rapidly dividing cells, but also of the embryonic or stem cells which are still due to undergo cellular differentiation.*[41] This can be shown when one observes the survival or the cytological alterations of these cells. The mature lymphocyte, however, which does not belong to either of these classes is an exception to this rule; its great sensitivity to radiations[283,284] is not well understood but may be related in some way to the fact that the nucleus is surrounded by unusually little cytoplasm which may diminish spontaneous recovery mechanisms or to the fact that it is a cell with a very short life-expectancy. It is also sensitive to many other stimuli. The situation is different from that in the spermatozoon, whose haploid nucleus plays an important role both in cell division and in differentiation processes which do not occur in the case of the lymphocyte, whose diploid nucleus may be more resistant than the sperm nucleus.

Mutations in multicellular organisms

123. Genetic mutations are found when gametes or the cells they originate from have survived irradiation and undergo fertilization.[285,286]

124. Many mutations are not lethal, and genetic abnormality of one of the gametes is believed to be the cause of many forms of congenital malformations: in this case, embryonic development is only very locally inhibited, and this leads to abnormalities such as harelip, cleft palate, spina bifida or the many deficiencies of the nervous system like congenital blindness, deafness or mental deficiencies. Hereditary diseases due to well defined biochemical deficiencies are also known to occur in mammals, and in a few instances they have been quite thoroughly analysed: in man the missing enzyme has sometimes been identified, as in galactosemia[288] and in phenylpyruvic oligophrenia[287], a form of mental deficiency related to abnormal phenylalanine metabolism.

Mutations in somatic cells

125. Mutations in somatic cells will affect the lineage of these cells but will not be carried to the offspring. These mutations have been shown to take place at a frequency of the same order as that found in the germ cells before meiosis (gonia)[25,289,290,291] and they have been found to occur in irradiated tissue culture; such mutations might play an important part in the determination of malignant growths.

126. It is very probable that the mechanism of mutation in higher organisms is very similar to that in micro-organisms; and the importance of fundamental studies in bacteriophage, microbial or fruit-fly genetics is that they enable us to get answers much more rapidly and in much better defined environmental conditions than can be hoped for in the case of the higher animals. Tissue culture, which is complex in the case of these organisms, may become of primary importance for the study of genetical mechanisms in mammalian cells, since such studies have become possible by culturing isolated mammalian cells in the same way as micro-organisms: mutations have been induced in such cultured cells.[292,231] Many somatic effects may have their origin in such mutations or in chromosome damage of non-germinal cells either as a result of death or loss of specific cell functions.

Carcinogenesis and other somatic effects

127. These effects, as well as their possible genetic origin, are discussed in chapter V and in annex G.

VI. Variables in radiation effects

Physiological conditions

128. Physiological conditions may vary in many ways and this can influence radiation responses.[41]

129. *During cell division (mitosis and meiosis)* there are different phases of radiosensitivity which one has attempted, not too successfully so far, to link to the different phases of new chromosome formation and nucleic acid synthesis which occur during these events. The survival of cells, the incidence of mutation and the alterations of chromosomes all undergo striking changes in radiation response, depending on the stage of the division cycle during which the organisms are irradiated, but it is difficult to generalize as to which is the critical stage since it can vary from one effect, or from one organism, to another.[227,293,294]

130. The induction of abnormalities or the lethal effect in developing embryos after irradiation of immature gametes of either sex, is strongly dependent on the stage of gametogenesis during which irradiation takes place. The first *meiotic* division is the period when it is possible to induce the greatest number of dominant lethals in the mouse oocyte.[278] In the case of the male, spermatogonia are the most sensitive and it seems that the degeneration occurs during the interphase or the first prophase following irradiation. The period of greatest sensitivity for various effects induced during embryonic development need not be identical.

131. *The age of cells and organisms* may affect their radiosensitivity: in an aged *bacterial suspension*, when the cells have reached their stationary phase, they become less sensitive to radiation;[295] but what is usually called an old culture is simply an "undernourished" one which has ceased to divide because the stationary phase only begins when some nutrient begins to be deficient; modern continuous cultures in media constantly renewed. By means of the chemostat might help to demonstrate whether aging occurs in micro-organisms or cellular suspensions of dividing cells of more complex organisms. The possibility of aging would exist if the daughter cells were not identical; and such a condition would arise if cytoplasmic material endowed with genetic continuity were not distributed evenly between daughter cells. It is probable that in aged cultures the radioresistance is greater because the bacteria have stopped dividing.

132. In the case of *higher organisms*, there is usually a great sensitivity during foetal life and the LD_{50} is less than half that of the adult, and, as has been already shown, the type of lesion depends on the time of embryonic development during which the radiation is delivered. In certain strains of mice, 200 r on the ninth day of gestation is 100 per cent lethal; on the tenth day, twice this dosage is required and after birth greater dosages still are needed. The sensitivity continues to decrease until adult life is reached: the LD_{50} is 500 r at forty days and reaches 670 r at 140 days for CAF_1

mice.[296,297,298] The sensitivity then remains very constant up to the last months of life—when it again increases sharply. A similar pattern of response exists in rats;[299] *Drosophila*[300] and birds,[301] on the other hand, have a much more constant radiosensitivity throughout their adult life.

133. These variations of resistance with age may be due to changes in mitotic rate (there are no divisions of somatic cells in *Drosophila*) or to changes in metabolic activity of different tissues, or to the fact that foetal tissues are undergoing active differentiation, or because the recovery processes of the aged cells have become inefficient.

134. *Nutritional and other physiological conditions.* Starvation of micro-organisms may render them more resistant, as seen in paragraph 131, but in other instances, or in reference to other types of effects, they can become more sensitive: fermentation by yeasts cultivated in a medium poor in ammonium salts is inhibited by doses which do not affect the same process when these nutrients are normal.[302]

135. There are few data on the effects of nutritional conditions on the radiosensitivity of the mammal, although a certain number of radiation effects concerning adrenal metabolism (weight, ascorbic acid, cholesterol) have the same sensitivity after one or seven days fasting.[303]

136. *Other conditions:* Anaemia apparently renders mice more sensitive to radiation, as is shown by the lower LD_{50} of certain anaemic strains. Exercise, on the other hand, does not seem to have much effect in mice.[304] It is possible, however, that in human populations, undernourishment and strain may affect the recovery processes.

137. *Oxygen tension.* The irradiation of water solutions in the presence of oxygen results in the formation of D_2H^0 radicals, in addition to H^0 and OH^0. This radical could also be formed *in vivo*. This would explain that when the *oxygen tension is diminished*, a lower response to irradiation occurs;[305] this is true for the survival of mammals,[306,307] and of birds,[308] for certain mutations[309,311] but not all,[310] for chromosome damage,[312] for various effects on embryonic development[313,280] and for certain biochemical reactions dependent on oxygen. Chemical metabolites or poisons whose presence in tissues reduces the oxygen tension may have similar effect. Lowering the oxygen tension may reduce the response to irradiation by a factor of 3 to 5 in the case of high energy radiation having a low ionizing density (X and γ rays, fast neutrons); when the oxygen tension is increased, these effects are not enhanced, which indicates that in air the oxygen tension is sufficient for the maximum effect. In the case of the densely ionizing α particles or slow neutrons, there is no oxygen effect.[305]

Comparative radiosensitivity of living organisms

138. When the survival rates after irradiation of different types of living organisms are compared, the sensitivities are found to vary very widely.[314] Mammals appear to be the most sensitive of all classes of organisms and doses able to kill 50 per cent of animals in thirty days ($LD_{50/30}$) range from about 200 rad for the guinea pig to 900 rad for the rat, the best estimate for man being 400 ± 100 rad. Cold blooded animals have an $LD_{50/30}$ which can rise to 3,000 r for the triton and perhaps 20,000 r for the snail. Bacteria and other micro-organisms cannot be compared on exactly the same basis, but it often takes as much as 100,000 r or sometimes much more to prevent 50 per cent of the organisms of many species from developing colonies, and certain protozoa may need more than 300,000 r to kill them.

139. Various factors may explain these differences. In cold blooded animals, either low *metabolic rates* or low cell division rates imply that radiation damage will take longer to develop; but this will not hold true for micro-organisms, which divide much faster than mammalian cells and resist much higher doses.

140. There may also be varying *oxygen tensions* in different organisms which could account for different radiosensitivities.

141. In the same species, organisms of different *genetic strains* may vary in radiosensitivity to lethal effects. This has frequently been observed in micro-organisms but it holds true also for mammals, where different strains of mice have different $LD_{50/30}$.[318,319] It has also been shown that similar genes in different species of *Drosophila* may mutate at rates which can differ by a factor as high as 2.[236,315,316] It has furthermore been shown that the frequency of production of developmental abnormalities may depend very much on the genetic strain: in Balb.C mice, certain malformations of the spine occur in 100 per cent of animals irradiated with 200 r during the 8th ½ day of gestation, whereas in the hybrid (C57×NB) F_1 no such malformations occur.[317] *For practical purposes, this means that observations obtained from one human population do not necessarily apply to a genetically different population.*

142. In some organisms such as adult insects where no cell divisions take place, one expects, and finds, a higher radioresistance; but in this case the gonads, where cell divisions do take place, appear also to be rather radioresistant; on the other hand, we have seen that embryonic cells may be very sensitive,[320] as in grasshoppers.

143. The presence of natural radioprotectors may be yet another factor: some organisms like insects are known to have a higher concentration of aminoacids (which are fair radioprotectors) in their body fluids. The degree of oxygenation of the tissues should also be taken into consideration.[320]

144. Finally, the number of sets of genes (*ploïdy*) has certainly something to do with radiosensitivity, as has been demonstrated for yeast and certain other micro-organisms, in which diploïd strains (containing two sets of genes) are more resistant than haploid ones (containing only one set).[320,321] Not only the number of sets of genes, but the number of chromosomes and their length appear to be important; the greater their number or the shorter their length, the more resistant the organisms seem to be. This holds true at least in the case of the plants which have been studied in this respect.[322]

145. Many of these suggestions are mere working hypotheses and nothing systematic has ever been done to find out about these different factors. Work in this direction may lead to the discovery of better ways of protection.

Adaptation to radiation

146. Little is known about the possibilities of organisms becoming adapted to radiation; the following suggestions may however be made.

147. Increase in catalase (an enzyme destroying hydrogen peroxide and possibly neutralizing other peroxides) in algae from the Bikini area has led to the hypothesis that this might be the result of some adaptive enzymatic processes induced by the unusual amount of peroxide detectable in the sea water.[323]

148. *Selection* might be expected to lead, in certain populations of mixed species, to the predominance of the most resistant strain. Furthermore, it is quite conceivable that irradiation itself induces a mutation which increases or decreases the radiosensitivity of an originally homogeneous population of cells. However, work done on *Drosophila*[236] and yeasts[324] does not indicate that breeding in a high radiation background leads to the appearance of more resistant genes. The UV irradiation of E Coli B, on the other hand, has selected a small number of radioresistant mutants (B/r)[259] occurring in normal cultures as a result of spontaneous mutations with the rate of about 1×10^{-5} mutations per bacterium per generation; one would expect that under chronic irradiation one could select this strain to some extent.

149. Tumours have often been claimed to become radioresistant when treated with X-rays; it is however difficult at present to give any sound explanation for such a behaviour; adaptation of the cells has been given as one reason[325,326,327,329] but it is difficult to dismiss the fact that the oxygen tension may decrease as a result of pathologic changes in the blood vessels and that the polyploidy of the tumour cells may enhance their radioresistance.

150. Another possible interpretation is that tumour cells may become incapable of further cell division *in vivo*, although when cultured they can resume division. Recent experiments tend to indicate that small dosages of X-rays (25 r) to embryonic mice makes them somewhat more resistant to exposure to X-rays during their adult life; this is however true only for females, the males appearing on the contrary to be adversely affected.[328] This apparent beneficial effect of low doses of X-rays on females is compensated by the fact that the number of litters they were able to bear fell from 5 for the control to 0.5 for the 80 r group; furthermore the number of young per litter was also greatly reduced —it may therefore be the fact of not bearing offspring which is responsible for the increase in life-expectancy.[330]

151. The study of the biology of species living in regions of high natural radioactivity may lead to some information concerning this problem. However, such work, although it may lead quite rapidly to definite ideas concerning the behaviour of short lived organisms or to the identification of pathological symptoms in man, will need to be carried on over many years or decades for the reactions of humans to such conditions to be understood. The mechanism of possible changes in these populations will need to be worked out in the laboratory where genetic strains as well as experimental conditions can be accurately controlled.

152. In certain experiments, the conclusion has been drawn of the favourable effect of small doses of radiation ("biopositive influence", "stimulating effect") both from external and internal sources.[331,332,333] However, further analysis usually explains this as a consequence of pathologically shifted functional equilibrium, where one biological function, taken in isolation, may appear to be stimulated. Also, the possibility of stimulating the initial stages of plant development and growth, followed by higher crop yield, is reported with various contradictory results.[334,335,336]

Secondary effects

153. One important problem is to know whether irradiation applied to one site of a cell or organism can induce an effect in another part.

Nuclear cytoplasmic relationships at the cellular level

154. Such secondary effects can be expected on account of the close physiological relationship between the different cellular organelles. It is known that if the normal isolated nucleus of an amoeba is put into the irradiated cytoplasm of another amoeba that had previously been enucleated, mitosis is inhibited in the reconstituted amoeba at cytoplasmic dosages only three times those producing the same effect in a normal organism.[337] It has also been shown that unspecific chromosome damage can be induced in an intact frog oocyte nucleus introduced in the irradiated cytoplasm of another oocyte[338] and ultra violet irradiation of the cytoplasm of the giant unicellular *Acetabularia Mediterranea* induces very rapidly some cytochemical alterations in the nucleolus which had been shielded during irradiation (this last effect is hardly apparent in the case of X-rays).[339] However, nuclear damage to *Acetabularia* is also demonstrated if only the nucleus is irradiated. In the course of experiment on eggs of *Drosophila*, the much greater sensitivity of the nucleus when directly irradiated is evident: it takes much more energy to kill the offspring by irradiating the cytoplasm of the egg alone than by irradiating the nucleus;[340] the same holds true for attempts to induce chromosome damage by micro-irradiating other parts of the cell.[341] Primary nuclear damage appears to play a prominent role in processes where nuclear activity is important as in cell division, mutations or many lethal effects. However, this does not mean that the cytoplasm does not participate in radiation damage. In some cells where no division occurs, cytoplasmic processes may become efficiently inhibited; this is the case of non-nucleated cytoplasms of *Amoeba* and *Acetabularia* which survive for shorter periods than if they contain a nucleus;[202,342,343] In this case, the role of the nucleus could be associated with some repair processes which cannot take place as efficiently in its absence, perhaps on account of the fact that the synthesis of cytoplasmic ribonucleic acid becomes seriously impaired in cytoplasm which has been deprived of its nucleus for some time.[171]

Peroxide formation in irradiated cells

155. One of the possible agents for these secondary effects could be organic or other peroxides arising during irradiation. It has been found that bone marrow cells incubated *in vitro* produce peroxides when the cells originate from an irradiated rabbit.[344] The significance of this finding is difficult to understand on account of the fact that many tissues (although not bone marrow) from non-irradiated rabbits also produce peroxides *in vitro*. Not much is known of the effects these peroxides might have on other cellular populations. It has, however, been demonstrated that many lysogenic bacteria show a diminished response when put in the presence of catalase (catalase reactivation after U.V. and X irradiation).[345] Another argument for the formation of peroxides in irradiated organisms is that even with small dosages (17,000 r) to yeasts grown in anaerobiosis, these organisms synthesize catalase or peroxidase when kept in

anaerobiosis, a condition during which they normally only have traces of the enzymes.[346] The synthesis of new enzymes is believed to be induced by peroxides formed during irradiation.

156. Radiation is also capable of inducing the formation of peroxides outside the cells, and irradiation by X or U.V. rays of organic culture media is mutagenic for the bacteria which are cultured afterwards; the effect can be prevented by catalase.[347]

Multicellular organisms

157. It has been found repeatedly that the *nucleic acid metabolism* of a carcinoma is temporarily decreased as a result of irradiation of the animal bearing it, although it had been completely shielded during the irradiation.[348,349] It has also been demonstrated that tumours originating from non-irradiated thymus cells can develop if these cells are grafted on a totally irradiated host whose thymus had previously been removed;[350] damage (by radiation or other means) or removal of the thyroid may lead to pituitary cancer.[351] No final explanation of effects of this type can be given; the first mentioned could be due to diffusible organic peroxides produced during irradiation and very small quantities of peroxides have been found in irradiated mice.[352]

158. On the other hand, normal regulatory processes located in the irradiated part of the animal can certainly be affected: hormonal effects, which are dealt with in chapter V, must be considered.[353] Stimulation of the pituitary as a result of thyroid disfunction is probably the cause of the pituitary tumour mentioned above (paragraph 157). *The exact relationships between hormones and biochemical processes in normal organisms should be known to understand many effects of radiation in the mammal.*

VII. Alterations of radiation effects by foreign agents

Protection

159. *Protecting agents* are those whose *presence during irradiation* decreases the response of an organism to radiation. Many experiments reported earlier (paragraphs 38, 42 to 47) constitute a basis for finding chemicals capable of protecting living organisms against radiations. However, our ideas on the mechanisms of protection *in vivo* are often conflicting, for the simple reason that the fundamental processes of radiobiology are not understood.

160. The idea of protecting organisms against radiations arose about a decade ago, as a result of the discovery of the indirect nature of radiation effects on dilute solutions. However, as stated earlier, it is very much doubted at present whether effects of radiation on organisms necessarily occur through indirect mechanisms. It can furthermore be expected that the relative contribution of direct and indirect mechanisms will vary for different biological effects and in each case the possibility of protection may thus be different.[355,356,358]

161. There are many possible ways by which radiation damage might be diminished: (*a*) loading the organism with chemicals capable of reacting with H^0, OH^0, and O_2H^0 radicals may divert these from reacting with important cellular constituents; (*b*) protecting agents could also act by covering the sensitive site of cell constituents, and this type of mechanism could be operative both for direct and indirect effects;[357] (ch) all agents capable of decreasing the intracellular oxygen tension can be expected to afford protection against direct or indirect effects which are oxygen dependent;[354] (*d*) finally, a protector might conceivably give more chemical stability to a macromolecule and favour the rejoining of broken bonds or divert energy from it. It is, however, at present very difficult to choose between any of these possibilities.

162. Very many experiments have been performed, very many chemicals have been tested and many effects have been found susceptible of a certain amount of protection.

163. The *survival* of unicellular and multicellular organisms have been quite considerably increased by the use of various agents. *SH* and *amino reagents* (cysteine, cysteamine or cystamine, glutathione) or the methyl derivative, methionine, as well as thiourea have been used successfully on micro-organisms and mammals.[355,356,358] Very similar possibilities have been found with S-2-aminoethylisothiuronium . Br . HBr (AET)[118] which is less toxic and may thus be used in many mammals, including monkeys and dogs.[359] As far as is known, there have been no attempts to use this compound in man. Further analysis has shown that at neutral pH a rearrangement of the AET to guanidine form occurred, so that the effective compound was 2-mercaptoethylguanidine hydrobromide (MEG).[360]

164. These protecting agents appear to have greater efficiency in promoting recovery processes rather than in preventing the initial damage observed: this is most striking in the case of the white blood cells and of the metabolism of spleen nucleic acid which seem to follow a similar pattern of response.[361]

165. The *number of chromosome aberrations*[161,362,367,368,369] and in some instances the *number of mutations*[118] have also been reduced when similar protective agents were used during irradiation. Successful experiments on plant cells have been reported, but cysteine does not reduce chromosome aberrations in mouse thymus,[363] although nucleic acid integrity does appear to be protected by thiourea or cysteamine[366] in the same organ. In *Drosophila*, however, and in micro-organisms, mutations have not so far responded to the protective action of cysteine or cysteamine.[364] In micro-organisms a protective action probably exists, but it is often difficult to interpret the experiments because increased survival as a result of protection could lead to an enhanced opportunity for a mutation to become expressed.[118]

166. These agents have in common the properties of having an amino-group and a sulfur atom (which often is in the form of a sulfhydryl group) and both these are believed to be important.[370] However, they can act independently because many amines are also found to be satisfactory protectors in the absence of a sulfhydryl, and a sulfhydryl group alone may be efficient in some instances.[370,371,372] It has often been suggested that the sulfhydryl group decreases the intra-cellular oxygen tension and this has been found to be the case in few living systems protected with cysteine or cysteamine.[129]

167. Many other agents have been used with a varying degree of success and the mechanism of action of some of these does seem to be dependent on the decrease of cellular oxygen, as in the case of the protection of micro-organisms with hydrosulfite.[20] A certain number of natural metabolites (succinate, glucose, alcohol) have protecting properties in a few instances, probably by consuming the cellular oxygen in the course of their

normal enzymatic oxidation.[118] Anoxia can also be obtained with a certain number of drugs like morphine which depress the respiratory centres: in that case a protecting effect is also found.[373] Cyanide, a strong inhibitor of respiratory enzymes, has been found to be an efficient protector of mice, although it would tend to increase the intracellular tension of oxygen.[374] On the other hand, seeds irradiated in its presence show a greater mutation rate when it is used in low concentrations, but a smaller one when the concentration is increased.[375] However, in these conditions an increased number of chromosome breakages is observed.[376]

168. It is not clear at present to what extent the protection is complete, because although damage is not lethal it may well be present and only become apparent at a later stage. It has been shown that rats, protected during irradiation, develop a large number of tumours;[377,378,379,380] these might have developed in the non-protected animals had they lived, as in the case of mutations in micro-organisms; and it is difficult to know if the primary events of induction of cancer have or have not been diminished. Nothing much is known on the protection against other late damage or against the early aging of irradiated organisms.

169. Protecting agents are much less efficient in the case of alpha rays or neutrons.[381,382] As was seen (paragraph 37) in these cases reduction of the oxygen tension is not expected to have any effect.

Sensitization

170. Radiosensitizing agents have been used in cancer therapy, but the fundamental aspects of sensitization are certainly much less known than in those in the case of protection. There are a few instances of enhanced reactions to irradiation in the course of *in vitro* experiments,[383] but these are not at present susceptible to application *in vivo*. It has, for instance, been shown that the oxidation of ferrous sulfate by X-rays is enhanced in the presence of various alcohols or of benzene.

171. As a result of the systematic study of many chemicals, it has been found that *synkavit*,[384] a derivative of vitamin K, increases the radiation induced mitotic inhibition in chick fibroblasts cultured *in vitro;* this effect was carried on in the absence of synkavit for several generations; and if rats are treated with the compound before irradiation their mortality is increased. Synkavit is also capable of increasing the permanent regression after irradiation of experimental tumours in the rat or of cancer in man. All that is known about the mechanism of action of this agent is that it becomes concentrated in the tumour as compared to the other tissues and that in tissue cultures its effect can be abolished by guanosine; this may indicate some interference with nucleic acid metabolism. If one increases the oxygen tension of tumours where it is usually low, one increases their radiosensitivity, a finding which has proved to be useful in cancer therapy.[385]

172. It is not known to what extent natural radiosensitizers might accumulate during certain steps of normal metabolic processes and thus alter the radiosensitivity.

Recovery

173. When organisms are irradiated, many processes, inhibited at first, recover. The synthesis of desoxyribonucleic acid is often decreased immediately after irradiation, but only temporarily; other biochemical effects which appear later are also temporary and display apparent recovery. In irradiated mammals, bone marrow and gonads can recover at the expense of the surviving cells which multiply and repopulate these organs, but permanent damage, leading for instance to more rapid aging, to an increased radiosensitivity or to the development of cancer, may have been established.

174. The lapse of time existing between irradiation and the biological expression of the primary damage, gives an opportunity of preventing the development of the lesion or of enhancing the spontaneous recovery processes.

175. *Recovery agents* are those which are effective when given *after irradiation*. Various methods for promoting the recovery of irradiated organisms have been described and can roughly be classified into two groups:

176. (*a*) *Those whose object is to destroy some intermediate compound* before the damage is definitively established: as in the *photorestoration* of a great number of effects of ultra-violet light,[386,388] the *catalase restoration* of lysogenic bacteria treated with ultra-violet light[340] or, in one instance, the effects of X-rays.[387] The first of these processes, in the case of ultra-violet irradiated bacteriophage is only possible if illumination takes place in the presence of extracts of normal bacteria; the second appears to lead to the destruction of organic peroxides formed during irradiation.

177. Restoration achieved in some instances by cooling or heating the irradiated cells[388] may inhibit the expression of injury before it is definitively established but none of these mechanisms is properly understood.

178. (*b*) *Those whose object is to replace a damaged compound or cell.* The provision of nutrients to micro-organisms which have lost the capacity of synthesizing them could be considered as one possible mechanism of recovery; recovery is however only apparent, because the fundamental damage has not been removed.

179. True recovery would depend on the possibility of replacing the damaged molecules or cells by non-irradiated ones. Experiments on bacterial transformations or on genetic recombinations in micro-organisms have shown that it is possible to control some alteration of their genetic characters. The mechanisms of the greater radioresistance of diploid compared with haploid cells may well have their origin in closely related mechanisms. On these grounds, the use of intact desoxyribonucleic acid to replace the irradiated compound inside the chromosome becomes a possibility. One successful experiment of saving ultra-violet irradiated Salmonella with intact DNA has been reported.[389]

180. It is possible to replace whole cell populations of irradiated animals and thus promote their survival; this can be done by injecting intact bone marrow from a non-irradiated donor into the circulation of a lethally irradiated one. This type of experiment was at first performed as a consequence of the demonstration that the death incidence of mice was considerably decreased when hematopoietic organs (like bone marrow of the hind limb, spleen or liver) are shielded during irradiation. Bone marrow injections have since proved to be successful in dogs, hamsters, monkeys.[391] Only tissues containing cells capable of forming granulocytes (mostly polymorphonuclear white blood cells), red blood cells or platelets are capable of this activity. These cellular suspensions are effective in preventing acute death from X or γ rays but apparently death caused by neutrons is much more difficult to prevent.[390,391,392,393]

181. As a result of injected bone marrow, the blood cells and platelets tend to reach normal values again, the weight of the body, of the thymus and spleen increases and immunological defence which had disappeared also becomes functional again. However, many of the lesions caused by radiation are not diminished after bone marrow injection: the greying of hair is not influenced and the fertility of gametes is not restored,[395] tumours develop with greater frequency in protected or parabiotic animals[396,397,398] and the normal life-expectancy of the animal remains decreased.[394] All these facts seem to demonstrate that only acute death has been prevented by the graft.

182. Important immunological problems are brought up by such experiments as they were in the case of the first blood transfusions: it is well known that mammals are only able to accept definitively grafts from subjects belonging to the same genetic strains (isologous grafts). For instance, one has known for a long time that grafts from one human being to another (homologous grafts) are usually eliminated rather rapidly, as in the case of skin grafts; this is also the case when grafts are made between different species of animals like rats and mice (heterologous grafts). This incompatibility originates from the fact that mammals possess immunological defence mechanisms which make them synthesize new antibodies to any foreign protein entering their blood circulation. However, it has been found that the immunological response of mammals is strongly inhibited in the days following total body irradiation, and in these circumstances both homologous grafts (from other strains of mice) and heterologous grafts (from rats) of bone marrow are capable of saving lethally irradiated mice. Cells of the donor animal have been characterized in the receptor animal by specific genetical or immunological identification;[390,399] and the repopulation of the myeloid and of the lymphoid tissue has been demonstrated. In the case of heterologous grafting of thymus tissue from rats into irradiated mice, the cells appear at first to be exclusively of rat origin but the later appearance of an agglutination reaction with specific mouse antisera indicates that thymus cells of mouse origin may be recovering.[400]

183. The survival of the animals injected with bone marrow becomes, however, dangerously compromised after a certain time, because, whether homologous or heterologous grafts are used, the incompatibility between these and the cells from the receptor animals reappears. The discussion has arisen as to whether the recovered cells from the irradiated organisms are again able to synthesize antibodies against the injected cells or whether these are making antibodies against the cells of the irradiated host.[401,402]

184. There have been recent attempts to stimulate bone marrow regeneration. It has been shown that alkoxyglycerols obtained from bone marrow, as well as some of their derivates, stimulate the white blood cells counts of patients irradiated for therapeutic purposes; this increase seems to concern the neutrophil polymorphonuclears and has also a beneficial effect on the platelet count.[403] It has also been found that the bactericidal properties of the blood serum were diminished in irradiated rats; this could be due to a loss of properdin, presumably a natural non-specific antibody. Treatment of these animals with a fraction from serum rich in properdin appears to increase the survival.[404,405]

185. Experiments on cell transfer have been made in attempts to replace leukemic cells, which can be destroyed by high dosages of irradiation, by normal marrow tissue with the hope of preventing further development of leukemia. Experiments performed on mice have shown that such a treatment is capable of increasing considerably the survival time of experimental leukemic mice.[406] One such attempt is now being made in a case of human leukemia.

186. The multiplication of donor cells in the irradiated host has unquestionably been established; however, this does not necessarily exclude a possible effect of subcellular fractions. The idea of the possible recovery capacity of bone marrow or spleen nucleoproteins was put forward a few years ago but was later abandoned on the ground that a small number of intact cells were present in the fractions injected.[407] It is, however, not possible at present to exclude the possibility that sub-cellular fractions do play a role in these recovery phenomena and, on account of the tremendous importance of proving or disproving this hypothesis, both for fundamental and applied purposes, work on the biological activity of nucleoproteins in normal or irradiated mammals is of great interest and should certainly be very actively pursued.

187. It will probably become possible to enhance similar recovery processes in human beings, but this *will* certainly require a much better understanding of immunological processes and of interactions between cellular populations before it becomes a reality.

VIII. Conclusions

188. Radiobiology has certainly made great headway within the last fifteen years. It has had, like cancer research, strong governmental support in many countries, and both these aspects of medicine have the common feature that *many* cellular mechanisms appear to be simultaneously concerned. This is why effects of radiation are as diverse as are cellular functions. The visible damage will probably depend on which particular mechanism is most sensitive at the time of irradiation, on its relative importance to the over-all economy of the cell and on the possible interference of other less damaged processes. Mutations, carcinogenesis, and the inhibition of mitotic activities, of cellular differentiation and of immunological processes, to name but a few examples of radiation damage, affect extremely complex cellular mechanisms, which, despite the efforts of many able scientists, remain one of the most provocative challenges. It thus becomes vital, if effects of radiation are to be understood and possibly prevented, that the functioning of normal cells and the organization of cellular populations be known. Radiobiology is not a science in itself; it is but an applied science and it rests entirely on our knowledge of the great principles of biology which cannot be studied independently of one another. The understanding of some aspects may at times progress more rapidly than that of others, but in the long run all these have to be integrated into one harmonious picture. The problem is not merely to push forward the study of genetics or of carcinogenesis, because it is obvious that these problems are dependent on most other aspects of cell physiology. Our ignorance of fundamental biology (taken in its widest possible sense) is undoubtedly the major factor limiting our understanding of radiation effects on man.

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Appendix

LIST OF SCIENTIFIC EXPERTS

The scientific experts who have taken part in the preparation of the report while attending Committee sessions as members of national delegations are listed below. The Committee must also express its appreciation to the many individual scientists not directly connected with national delegations whose voluntary co-operation and good will contributed in no small measure to the preparation of the report.

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