The Destructive Effect of Radiation on Lymphatic Tissue

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Summary

The destructive effect of radiation on lymphatic tissues is influenced in variable ways and to different extents depending on the physical factors concerned with the radiation itself and on biologic factors concerning the exposed organism. In this context the major physical factor is radiation dose and the major biologic factor is local versus whole-body exposure. Presence of non-neoplastic pathologic changes in lymphatic tissue could conceivably also alter radiation effects as well as the subsequent ability of the lymphatic tissues to regenerate. Regeneration in the exposed tissue is interesting from the normal physiology point of view, and the observation that granulopoiesis usually precedes reaccumulation of lymphocytes requires further consideration.

Potentiation of radiation effects by graft-versus-host and graft-versus-tumor reactions is of great interest because clinical trials utilizing immunotherapy of cancer as a supplement to standard therapeutic measures are now worth serious consideration. The idea that tumor cells of lymphatic tissue origin might cause graft-versus-host reactions could form the basis for additional experiments.

It is proposed that the organ system made up of lymphatic tissues be given the status of an organized academic branch of biomedical knowledge in order that basic and applied research in the field can follow some nonrandom scheme of development.

Introduction

Ionizing radiation has a profoundly destructive effect on normal lymphatic tissues in all mammalian species examined (27). Since radiation has the same destructive effects on the cells of Hodgkin's disease and of most tumors that originate in lymphatic tissue, radiation therapy for these neoplasms is an important part of the treatment program.

In discussing the mechanism of radiation destruction of normal lymphatic tissue, it is convenient to consider the variables involved under the 2 categories of physical and biologic factors. The physical factors refer to type of radiation, its quality and linear energy transfer, integral dose, dose rate, and similar parameters, whereas biologic factors are those of anatomic site, age, sex, hormonal condition, nutritional status, and related aspects of the irradiated organism or tissue. Regeneration after radiation injury also has several features of interest for this conference.

Radiation effects on lymphatic tissues overgrown by tumor cells of Hodgkin's disease are taken up in other papers presented at this meeting. It seems worthwhile, however, in the present report to mention radiation effects on some non-neoplastic pathologic or quasi-pathologic processes occurring in lymphoid organs, because these tissue changes could play a role in the pathogenesis of Hodgkin's disease or possibly have some effect on the outcome of therapy for the disease. I have in mind here inflammation, progressive tissue changes, circulatory disturbances (e.g., oxygenation), graft-versus-host reactions and responses to antigenic materials, and probably the general panorama of retrogressive changes other than simple necrosis. Presumably one could also, to be complete, take up the problem of radiation effects on lymphatic tissues that have experienced disturbances in development, now that gnotobiology and neonatal thymectomy have revealed hypoplasia of lymphoid organs in appropriate experimental circumstances.

Radiation effects on lymphatic tissues during the early stages of an immune response or during the remarkable proliferative phase of a graft-versus-host reaction should be of special interest according to the view to be presented later that the histologic features of Hodgkin's disease resemble a malignant immune reaction in the same general sense that Nicholson (42) thought skin cancer could be referred to as "malignant skin." This point of view about Hodgkin's disease has, as its consequence, the additional ideas that it is a disease of the germinal centers of organized lymphatic tissue and that either some antigenic stimulus is likely to be a continuing feature in its etiology, pathogenesis, and growth; or the opposite point of view, that some intrinsic change in the information mechanisms of the germinal centers has occurred in such a fashion that the cells behave as though they were experiencing antigenic stimuli or were unable to inactivate an antigenic stimulus.

Another matter of importance to the physician concerned with treatment of Hodgkin's disease is the potentiation of chemotherapeutic agents by radiation. Radiation potentiation of chemical injury in normal lymphatic tissue has received very little attention, but special interest is attached to the use of radiation in setting up graft-versus-host immune reactions in which massive destruction of normal lymphatic tissue occurs.

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Studies on Destruction and Regeneration

1. General Review

Organized lymphatic tissue and individual lymphocytes are extremely radiosensitive. This finding was reported within a few years after the invention of the X-ray machine. Dunlap (24) has reviewed the extensive literature on the subject that appeared between 1903 and the time of his paper in 1942 [see also Engeset (27)]. Subsequently, intensive restudy of the morphologic effects of external whole-body radiation and internal emitters on lymphatic tissues was carried out during the wartime development of atomic weapons. A detailed account, with many illustrations, of this work by R. G. Murray (41) and by P. P. H. de Bruyn (22) can be found in the Plutonium Project Record volume on Histopathology of Irradiation From External and Internal Sources edited by William Bloom (1948). Later reviews (4, 7) of radiation effects on the lymphatic tissue system refer to Murray and de Bruyn as standard descriptive works in this field.

The striking effect of a single 950 r whole-body exposure in reducing the size of normal lymph nodes in mice is shown in Chart 1. Histologic appearance of an irradiated node at 3 days, after the products of necrosis have been removed, is illustrated in Fig. 1. The effect of the large acute exposure to ionizing radiation is to destroy the parenchyma of the lymph node, leaving intact the stroma, blood vessels, mature plasma cells, and reticulo-endothelial (phagocytic) cells. The parenchyma refers to the cortical masses of tissue lymphocytes and the dividing cells in the germinal centers. A few lymphocytes usually remain scattered through the cortex, and stromal cores of the germinal centers are sometimes present in the tissue sections. The other organized lymphatic tissue in the spleen white pulp, Peyer's patch, tonsil, and thymus show the same picture of degeneration following irradiation.

Regeneration is an intriguing matter in lymphatic tissue because the order of reappearance of parenchymal elements usually follows that of the original development of lymphatic tissues during fetal and neonatal life, with collections of cortical lymphocytes being seen first, followed by germinal centers; the germinal center apparently first appears during development, during regeneration after radiation, or under any other circumstances as a result of adventitious or planned antigenic stimulus (Chart 1 and Fig. 2).

There is some evidence that functional regeneration of the lymphoid system after irradiation in the adult mouse depends on the presence of an intact thymus (21). The effect of an intact thymus on regeneration of malignant lymphatic tissue after irradiation has apparently not been studied.

The possibility that temporary extramedullary myelopoiesis in lymphatic tissues preceding their regeneration has some fundamental role in the regeneration process needs careful consideration. Presence of granulocyte-forming tissue in lymph nodes prior to regeneration or abortive regeneration has been particularly noted in bone marrow transplantation studies (Chart 1). It has also been observed in spontaneous regeneration (22).

In regenerating nontumor-bearing lymphatic tissues it is unlikely that any counterpart of regeneration of the irradiation-treated tumor cells of Hodgkin's disease exists. The reason for this is the short-lived nature of the dissociated growth of germinal center cells in the normal immune response (12). Regeneration of an injured dissociated growth process is not easy to conceive of, and in the present report Hodgkin's disease is interpreted to be a malignant counterpart of the dissociated growth of germinal center cells in the same manner as giant follicular lymphoma is at least superficially the malignant counterpart of the hyperplastic restitution of germinal centers that is seen a few days after immunization (8, 14, 32, 56). These tumor processes in lymph nodes are looked upon as "true" maturation arrests or a kind of imago. Plasma cell tumors and multiple myeloma have as their normal counterpart the optional plasmablast and plasma cell development that occurs after immunization with some antigens. I am inclined to consider all or nearly all primary tumors of lymphatic tissues as tumors of the germinal center or its cellular precursors, or its cellular descendants. Spread of these tumors is not infiltration or metastasis in the ordinary fashion because growth of the normal germinal center cells is expansive, infiltrating, and shows evidence of spread to distant sites, with probably a preference for other lymphatic tissues.

During regeneration of lymph nodes after whole-body irradiation, a process that might be called "acute lymph node tumor" has been seen infrequently (10) that is quite analogous to the phenomenon of acute splenic tumor (33, 44, 45). Presumably some adventitious (bacterial) antigenic stimulus has caused the "acute lymph node tumor" as an expression of the immune response in regenerating lymphatic tissue.
There are still other morphologic phenomena in irradiated lymphatic tissue that help complete the catalog of tissue changes that might be considered in a conference on Hodgkin's disease.

One of these is fibrinoid necrosis in foreign bone marrow radiation chimeras. There are deposits of eosinophilic material in spleen white pulp that superficial appearances are composed of fibrin, not amyloid (Fig. 3). Deposits of similar morphology can also be seen more rarely in lymph node and bone marrow. Because the donor blood-forming cells around these deposits are destroyed or lysed, the fibrinoid necrosis is interpreted to be a manifestation of local recovery of the host immune mechanism in the radiation chimera. 2

In lymph nodes or spleen, giant cell formation and reticuloendothelial proliferation also seem to be an expression of a focal recovery of the host immune mechanism with destruction of the foreign bone marrow graft in that particular region of the spleen or lymph node. An exaggerated expression of this process can be seen in the foreign bone marrow transplant experiment and is known as the "midlethal dose effect" (15, 54).

The last tissue reaction that requires special consideration in irradiated lymphatic tissue is the graft-versus-host reaction (12). When certain foreign bone marrow or lymphatic tissues are given to supralethally irradiated mice, a marked temporary enlargement of the damaged lymphatic tissues appears, followed by a secondary atrophy with the sudden cessation of the proliferative phase of the graft-versus-host reaction (Fig. 4). Very similar cellular proliferation can be produced in intact animals under the proper experimental circumstances (30), and immunologic tolerance in newborn animals is presumably induced by cellular proliferation of the same type (3).

The proliferative phase of the graft-versus-host reaction has a rather strong resemblance to dissociated growth of germinal center cells in the immunized intact animal, and both processes in turn resemble Hodgkin's disease histologically, with the exception that proliferation is only of a few days' duration in the 2 non-neoplastic conditions (Fig. 5).

Snell and Stevens (49) have suggested that a tumor derived from lymphatic tissue might be able to produce a graft-versus-host reaction, but this idea has not been developed further. It seems unlikely that any graft-versus-host reactions are involved in the ordinary transplantable lymphomas of mice. It also seems unlikely that Hodgkin's disease itself is a graft-versus-host type reaction, although this point might get further attention.

One transplantable tumor that gave a superficial resemblance to graft-versus-host reaction in the host was seen in guinea pigs carrying a radiation-induced acute fulminating leukemia (36). There was extreme lymph node involvement (Fig. 6).

The possibility of graft-versus-host reactions being caused by transplantable tumors needs further evaluation with techniques developed by Billingham, Brent, Medewar, and others.

In the preceding paragraphs destruction and regeneration of lymphatic tissues has been considered only in the context of whole-body exposure. Engeset (27) has reported comparison of lymph node reactions after whole-body and local irradiation. He found that the primary necrosis after 3000 r local irradiation is recovered from within a few hr and that for several days the irradiated lymph node appears nearly normal except for the loss of mast cells. In the ensuing weeks, however, an extreme secondary atrophy, apparently following vascular damage, develops with destruction of the lymph node and its original stroma. After whole-body exposure to much smaller doses, prolonged atrophy from the primary necrosis has been seen by many investigators.

Prompt temporary recovery after local irradiation has been interpreted to mean influx of normal cells from shielded lymphatic tissue, whereas with whole-body exposure there are no normal cells to migrate into the atrophic tissue. This explanation seems quite reasonable because rather spectacular regeneration of lymphatic tissues takes place within a few hours in total-body-irradiated mice when they receive an i.v. injection of lymphatic tissue cells (17).

2. Biochemistry

The biochemistry of necrosis has not been studied to the same extent as the morphology of necrosis; therefore there is no firmly established biochemistry of radiation necrosis in lymphatic tissues or any other organ system.

Baeq and Alexander (1) consider interruption of energy supply and the enzyme-release hypothesis as 2 main theories of the nature of the early biochemical lesion for effects of ionizing radiation on cells. Major biochemical consequences of radiation exposure are the interference with biosynthesis of nucleic acids and the special phenomenon of chromosome breakage.

In connection with the enzyme-release hypothesis there is an increase in nucleases in lymphatic tissues and other organs within a few hr after exposure, but the importance of the increase in catabolic and anabolic processes for understanding the earliest significant biochemical lesions is uncertain.

It is generally considered that the inhibition or delay in DNA synthesis is the single most important biochemical change in lymphatic tissues caused by radiation because one can presume that the ionizations are in some way affecting those portions of the cell genome that control DNA synthesis itself. Of all the genetic information present in lymphatic tissue cells it seems likely that the most fundamental genetic information concerns the task of achieving DNA synthesis (9).

It is this area of effects on genetic sites that should be evaluated in future studies on the mechanism of radiation injury to lymphatic tissues, since these sites have the information for initiating DNA synthesis.

Schrek and Elrod (46) report radioresistance of lymphocytes at low temperatures, but the unusual radiosensitivity of nondividing lymphocytes at body temperature has never been explained (43). It may be that the function of these cells involves their "necrosis" and that radiation somehow triggers their usual functional behavior. I once speculated that they represent labile stromal cells in the lymphatic tissue whose function is to hold space until antigenic stimulation occurs and the real actors, the germinal center cells, take over and carry out lymphatic tissue function. The great mass of tissue lymphocytes conveniently die or go away to make room. Needless to say, this idea has not caught on and many investigators think that the tissue lympho-

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2 For a more complicated story of progressive generalized amyloidosis in radiation chimeras see the paper of Bradbury and Micklem (5).
cytes are the important cells in initiating an immune response and that the germinal center cells play a secondary role (31).

The regeneration and development sequence in lymphatic tissues referred to earlier does suggest that lymphocyte collections usually precede the appearance of germinal center cells. It isn’t clear whether or not this also predicts the lymphocyte origin of germinal center cells.

3. Physical Factors

Many physical factors could be systematically investigated in radiation injury and regeneration after local or whole-body irradiation in normal lymphatic tissues. Such studies would create a wealth of new information that might be of considerable value to the radiotherapist concerned with Hodgkin’s disease. Exploration of physical factors, however, has been restricted to a few variables.

There is a clear dose-response relation for lymphatic tissue damage and repair when the radiation exposure is delivered over a short interval. An interesting finding that has received little attention is the failure of thymus weight to decrease as expected in the kilorontgen range of exposure.

Vogel and Ballin (55) made the original finding in rats that injury (as measured by weight and histology at 24 hr) to the thymus after whole-body or local irradiation between 10 and 30 kiroeontgens was less damaging than below 10 kiroeontgens, where injury was directly proportional to dose. Trowell et al. (53) confirmed the essential finding of Vogel and Ballin and, further, did not think radiation fixation of the thymus or inactivation of its autolytic enzymes could explain the paradoxical effect. Subsequently, Trowell (52) has investigated irradiation of the thymus in vitro and has found a similar paradoxical effect in agar cultures.

The superficial resemblance of the “Vogel-Ballin paradox” to reversal of seedling height in maize at very high radiation exposures [Schwartz (47), Schwartz and Bay (48)] was pointed out by Trowell (52). Similarly, McGrath and Congdon (39) considered the Schwartz experiment in explaining abnormal cytologic enlargement of intestinal epithelial cells after exposure to radiation.

Schwartz points to the finding that delay in cell division increases with increasing radiation dose. If death of the cell usually occurs during or after its subsequent division, then prevention of cell division would prevent ordinary radiation necrosis. Growth (protein synthesis, etc.) of the individual cells is not stopped by the exposure and seedling growth continues temporarily.

This interesting area of radiation biology can also be related to a concept mentioned earlier in this report: that radiation effects those parts of the cell that contain the information mechanism for initiation of DNA synthesis and cell division.

New interest in the effect of dose rate of whole-body exposure on lymphatic tissues is seen in the recent reports by Courtenay (19) and Gengozian (28), who found greater repair or less damage of immunologic function when the radiation was given at a low dose rate (1–4 r/min as compared to 29–54 r/min). Transplantation of foreign bone marrow, which was their goal, was less successful when the transplant recipients were irradiated at a low dose rate.

Dose rates in the range from 1.1 r to 8.8 r/8-hr day were investigated by Spargo et al. (50) for effect on morphological changes in lymphatic tissues. In this range it often took several months of whole-body exposure to produce discernible changes.

Type of radiation is an important physical factor. X-rays and gamma rays have been used more often for radiation effect studies than other types. However, using beta rays, alpha particles, and neutrons, Murray (41) and de Bruyn (22), found the same severity of radiation damage with the different kinds of radiation.

Because the quality or energy of radiation as well as the linear energy transfer (LET) varied greatly with the several types of exposure, it is concluded that these physical factors are likely to be associated with quantitative differences in radiation effects on lymphatic tissues rather than any qualitative alteration [see Bateman and Bond (2)]. Proton and meson effects on lymphatic tissues have apparently not been investigated.

4. Biologic Factors

Anatomic site is the major biologic factor in all radiation effects in mammals because of the remarkable variations in organ sensitivity. Within the lymphatic tissue organ system, however, all sites appear to be essentially equally radiosensitive. We have noted, though, that thymus regenerates faster than other lymphatic tissues (10, 11).

Extracorporeal irradiation of blood and lymph has been studied by Cronkite and his colleagues (20) for its effect on normal as well as neoplastic lymphatic tissues. This method of irradiation is interesting, not only because of the depletion of lymphocytes, but also because stem cells from the hemopoietic and lymphatic tissue systems that normally circulate in the peripheral blood are irradiated (29). Presumably their malignant counterparts, that also circulate, are also effectively irradiated, because the procedure has shown some therapeutic effectiveness in certain leukemias.

Factors of age, sex, hormonal conditions, nutritional status, and other variables operating within the range of physiologically normal values are not known to influence radiation destruction of lymphatic tissues. They might play a role in regeneration, but this point requires special investigation.

If other functional or pathologic parameters of lymphatic tissue injury such as immune response and tumor induction are considered, then these biologic factors operating within the normal or an exaggerated range can play a significant role in the consequences of the radiation effect. An example of this is the major effect of hormonal status on yield of radiation-induced tumors of the thymus in mice (34).

5. Other Tissue Changes

In the foregoing sections consideration has been given to radiation effects on normal lymphatic tissues and their regeneration. The present section is intended to point out that radiation effects on lymphatic tissue changes other than neoplasia could be of interest in a conference on Hodgkin’s disease.

Radiation effects on lymphatic tissues that have experienced disturbances in development or show regenerative changes have not been systematically studied, although, as mentioned earlier, neonatal thymectomy and germfree life yield hypoplasia of the...
lymphatic tissue system. The preliminary finding in these studies is a failure of the system to regenerate properly as measured by its immunologic function.

Congestion and other circulatory disturbances would be of interest to study. Considerable attention is now directed toward hyperbaric oxygen radiotherapy in cancer, and Wildermuth (57) has recently summarized work done in this field. Apparently the joint effects of hyperbaric oxygen and radiation on lymphatic tissues have not been studied, but the use of this method for Hodgkin’s disease and other tumors of lymphatic tissues does not need to await studies on normal lymphatic organs.

Ionizing radiation has been used in the treatment of inflammation, parasitism, and chronic infective granulomas [see Ellinger (26)]. Looking at the situation in another way, one can raise the question concerning the effects of radiation on lymphatic tissues when inflammation, parasitism, or granulomata are present in the tissues. Presumably radiation destruction and regeneration would be affected by the presence of these complicating tissue changes. In mice, parasites are often found in the mesenteric lymph node, where they incite chronic inflammatory processes that alter markedly the radiation effects in these areas. Progressive tissue changes consist of alterations like regeneration, metaplasia, and hyperplasia. How the presence of these basic tissue changes would influence radiation destruction and regeneration is not known.

So far as we know, the primary function of lymphatic tissues is immune response; and our general impression from histologic study is that adventitious immune reactions are nearly universally present in conventional animals (12). Radiation effects in normal lymphoid organs take place against a variable immune response background.

There is an extensive literature dealing with radiation immunology [see Taliaferro et al. (51), Makinodan and Gengozian (37)] that has not been evaluated in the context of our present conference. The findings in radiation immunology might contribute something to radiotherapy or some other aspect of Hodgkin’s disease.

Meaningful ideas might develop if a phase of radiation immunology dealt with chronic antigenic stimulation rather than the pulsed antigen administration that is usually studied.

One rather interesting finding is that a residual immune response exists after whole-body irradiation (12, 16). Serum antibody production is prevented by exposures less than 1000 r if the antigen and radiation are given at about the same time. However, with certain kinds of antigens it may take 3000 r to prevent all histologic evidence of an immune response (18). In this sense there is a residual component of the immune response that is extremely radioresistant. Some of the cells involved in the residual immune response have at least a superficial resemblance to the Reed-Sternberg cells of Hodgkin’s disease, thus contributing to the concept stated earlier that the disease is a kind of malignant immune response (Fig. 7).

Radiation effects on graft-versus-host reactions in lymphatic tissues could relatively easily be studied now that there has been considerable recognition of their morphologic features in mice (12, 13).

Splenic amyloidosis in mice seems to have some connection with absence of germinal centers (J. W. Goodman and C. C Congdon, unpublished data). Radiation effects on splenic amyloidosis probably should be examined for information which might contribute to our understanding of pathologic changes in germinal centers.

Radiation Potentiation
This topic might be easiest to look at as a restricted case of the more general problem of action of multiple injurious agents on biologic systems. Dual- or triple-action situations in biology and medicine are notoriously difficult to work with and understand.

In the present context radiation potentiation is taken to mean injury to normal lymphatic tissues by some agent with a potentiation of this effect by exposure to ionizing radiation. The condition in which some agent, such as increased oxygen in the radiation field, increases the radiation effect is also a facet of the potentiation concept and is usually thought of as radiation sensitization.

Substances that intensify radiation effects have been studied for many years (40). Synkavit, a phosphoric ester of a substance related to vitamin K, has been examined rather extensively for its radiation-sensitizing actions, but its use in clinical medicine has not been widely promoted [Bacq and Alexander (1), pp. 477-79]. Bacq and Alexander suggest that cells normally contain part of their physiologic processes radioprotective agents that control their usual radiosensitivity; radiosensitizing or radio-photomizing agents interfere with the action of these protective substances.

An interesting basic approach to the problem is to take a very radioresistant organism such as Micrococcus radiodurans and develop agents that increase its sensitivity (6).

Antimetabolites or any toxic chemical will make an irradiated animal sicker than when a single injurious agent is used, and many antimetabolites have been examined in microorganism or tissue culture systems. A histologic evaluation in lymphatic tissues has not been made, although there is good reason to do this. Antimetabolites combined with radiation have been studied for effects on the immune mechanism.

It was mentioned earlier that radiation effects on the thymus are increased by hormones and substances that injure the thymus when administered alone.

The extreme destructive effects of graft-versus-host reactions on lymphatic tissues deserve special consideration, and presumably a systematic examination of this immunologic reaction will eventually be made from the radiation potentiation point of view (Fig. 8).

In addition, as mentioned in the discussion, immunotherapy of cancer by means of graft-versus-host reactions is a topic that requires major consideration by cancer therapists.

Discussion
Even though this paper has been somewhat ambitious in scope, it still isn’t a comprehensive review of radiation effects on lymphatic tissues. Instead, my plan has been to call attention to findings in the radiobiology of lymphatic tissues that might be of near or even remote interest to a group discussing obstacles to the control of Hodgkin’s disease.

One of the first points to be made is that in spite of the rather bizarre histologic pictures that Hodgkin’s disease presents they
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seem to mimic the histology of normal and pathologic immune reactions in intact or irradiated lymphatic tissues. This suggestion immediately puts Hodgkin's disease into the framework of a malignant immune reaction that cannot be turned off, whereas normal and nonmalignant pathologic immune reactions are uniquely self-limited, at least from a histologic point of view. Either the tumor cells are driven by an unusual antigenic stimulus, or some lesion of information concerning initiation of cell division or turning off of cell division is present.

There is a particularly interesting neoplastic lesion in the mouse mesenteric lymph node that resembles Hodgkin's disease (25). It might well be studied with the above thoughts in mind. In addition, the concept of Hodgkin's disease being one of the germinal center diseases could be looked at in the mesenteric lymph node disease in mice.

Destruction and regeneration in lymphatic tissues require more intensive study in relation to all of the problems outlined in the present text. In fact, I feel this organ system is so important that it deserves a kind of specialty status in the sense that hematology is a specialty devoted to bone marrow function. It may be that a more systematic evaluation of the lymphatic tissue organ system in health and disease could develop as the essential content of this specialty or subspecialty. At the present time the closest thing to a field concerned primarily with study of lymphatic tissues is the growing area of experimental hematology. Increased interest in the biochemistry of lymphatic tissues is sorely needed.

Potentiation of radiation effects by graft-versus-host reactions in lymphatic tissues is clearly possible from the extensive research on bone marrow transplantation. Clinical experiments on graft-versus-cancer reactions have been considered or carried out for a number of years (38). We now think immunotherapy (graft-versus-tumor) may be a good idea to attempt in Hodgkin's disease to supplement the other forms of treatment.

The principal idea is to obtain fresh tumor tissue and use it to immunize a normal human or possibly a primate. After obtaining tissue the Hodgkin's disease patient would receive treatment to reduce the remaining tumor mass to as low a level as feasible. At this point systemic chemotherapy would be stopped and the patient would receive, i.e., thoracic duct lymphocytes in very large numbers from an immunized relative or other individual. The clinical experiment would be analogous to the immunotherapy of chemically induced sarcomas in rats reported by Delorme and Alexander (23). It is presumed that unique antigens or a virus, or both, might be present in Hodgkin's disease tumor tissue, and that temporary graft-versus-tumor reactions of a secondary response type might take place and destroy the residual tumor tissue.

The experimental demonstration of unique antigens has been limited so far to chemical- and virus-induced tumors in animals (35). However, nearly all tumors show disturbances in chromosomal karyotype; if this universal lesion has any connection with the antigenic changes now found in certain induced neoplasms, then a fundamental basis for the immunotherapy of cancer is clearly foreseeable.

Even though these speculative relationships are still unevaluated, I think one can justify proceeding with immunotherapy experiments in man in situations where chemotherapy or other methods give marked reduction in tumor mass but with inevitable recurrence of the neoplasm. There is no a priori reason for not trying immunotherapy as outlined above in other cancer cases, with the realization that the animal experiments suggest at this time a rather restricted cancer situation.

References

Effect of Radiation on Lymphatic Tissue


FIG. 1. Depleted lymph node 3 days after 950 r of whole-body X-ray. Note stromal core of germinal center near marginal sinus. H & E, X 250.

FIG. 2. Regenerating lymph node 12 days after 950 r and isologous bone marrow showing large mass of lymphocytes in the cortex and slight granulopoiesis in the medulla. H & E, X 250.

FIG. 3. Fibrinoid necrosis of the spleen white pulp 12 days after lethal whole-body irradiation and homologous bone marrow injection. H & E, X 250.

FIG. 4. Proliferation phase of graft-versus-host reaction in a lymph node 8 days after lethal whole-body irradiation and homologous bone marrow injection. H & E, X 250.

FIG. 5. Blurring of the white pulp in a normal mouse 2 days after an i.v. injection of sheep red blood cells. The process is also referred to as disassociated growth of germinal center cells. H & E, X 120.

FIG. 6. Fulminating leukemia in the lymphatic tissue of a guinea pig that was exposed to chronic whole-body gamma radiation. There is a superficial resemblance to graft-versus-host reactions. H & E, X 340.

FIG. 7. Residual immune response in spleen white pulp 2 days after 950 r of whole-body irradiation and an i.v. injection of human saliva. Note very large cells near middle of photograph. H & E, X 375.

FIG. 8. Peripheral lymph node destroyed by graft-versus-host reaction in an irradiated mouse 17 days after homologous bone marrow transplant. H & E, X 100.
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