

Part IV
CLINICAL—ABDOMINAL INFECTIONS

Chapter IV

EARLY STUDIES OF ROENTGEN THERAPY

As stated elsewhere, the treatment of infections was started immediately after Roentgen's discovery. Before 10 years had elapsed, much important experimental work had been completed and many accurate clinical observations had been made. As far as our interests are concerned, the outstanding experimental work was that completed by Heinecke¹ and some by Warthin. The latter's report, from which the following material is quoted, is instructive and contains many references to the early literature which should be consulted by those wishing more details.

In this same year (1904), appeared the important work of Heinecke, first as a preliminary communication and later as a final report. His research is by far the most important contribution to roentgen ray pathology. He studied experimentally the effects of roentgen ray irradiation on small and large rabbits, white mice, guinea pigs, and dogs, and found in all conclusive evidence of an elective action of the rays upon the lymphoid tissues of the spleen, lymph-glands, and bone-marrow. All mice exposed for more than five hours died within three to 11 days. The autopsies showed great emaciation, intestines distended and filled with fluid contents, spleen very small, darkly pigmented and showing no follicles. The microscopic examination of the spleen and lymph-glands showed an extensive destruction of lymphocytes, both in the pulp and follicles, also of the giant-cells (mice), polynuclear leukocytes and probably the eosinophiles also. In the bone-marrow there was a rarefaction of the specific cells. The spleen, bone-marrow, and lymph-glands ultimately became very poor in cells. There was also a marked collection of pigment and phagocytes containing red cells and pigment in the spleen and lymph-glands. These changes were found in all the lymphoid tissues of the body, intestinal follicles, thymus, etc. A latent period was not found. The changes were transitory, regeneration quickly taking place.

In 1905, Halberstaeder reported observations on the effects of roentgen rays upon the ovaries. He found them much more sensitive to the rays than the skin, and more so than the testicles. The irradiated ovaries showed great reduction in size.

The above abstracts represent the sum total, in so far as my search of the literature has been able to go, of our knowledge concerning the action of the roentgen rays upon the body tissues. It will be noted that the greater part of these observations are concerned with changes produced in the skin. With the exception of the recent work of x-ray

effects upon the sexual glands and Heinecke's important studies of the changes produced in lymphoid tissues, we are practically ignorant of the action of roentgen rays upon the deeper tissues and organs of the body. During the first five years of clinical work with the x-rays, it has been somewhat strenuously denied by a number of prominent x-ray workers that the roentgen rays have any effect upon the internal organs. Evidence has, however, been slowly accumulating to the effect that, aside from the purely local action, roentgen irradiation may produce changes in the internal organs.

The publication in 1903 (Senn), and the first half of 1904 (Brown, Bryant and Crane, etc.) of reports showing most remarkable results in the treatment of leukemia by roentgen ray irradiation, and the fact that such results had at that time no pathologic explanation, and as they promised to throw some light upon the pathology of leukemia and possibly also upon the origin of the various forms of white cells, led to the planning of the work early in the summer of 1904. Heinecke's first report (1903) had appeared, but was then unknown to me, and the experimental part of this investigation had been largely carried out before his complete study was published. Although repeating many of his experiments, my results are of importance not only in confirming his work, but because they offer much in addition to his observations and conclusions, the microscopic study having been carried farther. Further, having access to autopsy material of three leukemic patients treated by roentgen rays, I have been able to make a detailed study of the changes in the pathologic picture of leukemia resulting from such treatment, and to arrive at some conclusions regarding the nature of the action of the x-rays in this disease and of its therapeutic worth. These conclusions, it may be said in the beginning, are opposed to Heinecke's view that roentgen ray treatment might prove of value in diseases of the lymphoid tissues, particularly leukemia and pseudo-leukemia. Further, this research has added to our general knowledge of roentgen ray pathology and offers strong evidence of the occurrence of an intoxication caused by the disintegration of cells by the rays.²

In the foregoing quotation some interesting observations are brought out: the selective action of the rays on the lymphocytic cells, the analgesic effects of the rays and the beginning realization that the internal organs as well as the skin are affected by x-rays and that the ovaries were especially sensitive.

In later years, DesJardins³ again called attention to the early work of Heinecke and Warthin and to its importance in the treatment of inflammatory conditions. DesJardins' report, including an extensive review of the literature, should be consulted by anyone interested in radiation therapy of inflammations.

Hektoen's⁴ work in the experimental investigation of anti-

body formation following irradiation came a few years after that of Heinecke and Warthin. The tendency of the early workers, both in experimental and in clinical fields, to use excessive amounts of radiation in their work and the lack of instruments to measure correctly the amount of radiation used undoubtedly interfered with the progress they would have made otherwise.

STUDIES OF LYMPHOID REACTIONS

The work of Heinecke and of Hektoen was undoubtedly of considerable value to Murphy and Morton who, in 1915, according to Evans and Leucutia, while experimenting with cancer in mice, for the first time observed that regeneration of the lymphocytes is followed for a short period by increase in the number of lymphocytes above normal.

They also found that, in a few cases, such stimulation of the lymphocytes resulted from the primary reaction of small doses of roentgen rays. In 1919 Thomas, Taylor and Witherbee, and Nakahara proved that the stimulation of the lymphocytes follows the administration of small doses of roentgen rays of low penetration as a constant phenomenon, always accompanied by hyperactivity of the lymphoid centers. The lymphocytosis as a rule reaches its height on the fourth day following irradiation and then gradually subsides.

As a result of the above fundamental experiments, which later were supplemented by many others, three facts are now well established:

1. There is extreme sensitivity of the lymphocytic elements: both the circulating and the elements of the lymphoid centers, towards radiation. Too much radiation produces rapid destruction of these elements.

2. There is great regenerative and recuperative power of the lymphoid tissues.

3. There is a definite stimulation of the lymphocytic elements by small doses of roentgen rays.

These three factors, as we shall see, are of great importance in the radiation therapy of all conditions of the lymphoid tissues, and they are directly responsible for the many surprisingly good results obtained. They also explain to us why certain diseases, as, for example, tuberculosis or acute and chronic infections, respond more readily to irradiation when occurring in lymphoid tissues, than in any other part of the body.

It follows from this, that in treating lesions of the lymphoid tissues, destructive irradiation will be required in the cases where primary destructive action is needed, that is, in case of bulky tumors (neoplastic and their relative processes), while the stimulative irradiation will have a more beneficial effect on the inflammatory conditions (acute and chronic inflammations), where the secondary reaction, i. e., the protec-

tive mechanisms of the local tissues is of considerably more importance.

In both forms of irradiation there is, however, also a general effect, manifesting itself in a reaction, which may be called the immunization process. There are two factors concerned in this process: (a) The antibodies of the organism produced or stimulated by the action of substance liberated from destroyed pathological cells; (b) the lymphocyte stimulated to over-action by different biological, chemical and physical agents.

(a) The antibody production, if we may call it so, is always the result of the direct destructive action of some agents, mostly roentgen rays and radium, on the pathological cells. A disintegration of the cells with liberation of large quantities of chemical substances (toxins) follows, which in turn leads to an excessive formation of protective material (antibodies). That such a process exists is conclusively brought out by the serological experiments of Heidenhain and Fried in the case of radiation therapy of acute coccus infections. These experiments prove that the exposure of acute infections to roentgen rays is followed by a direct increase in the bacteriolytic power of the blood, lasting for a period of from four to six days. The pus removed from the irradiated lesion during the same period remains sterile. Helber and Linser demonstrated a similar process for the destruction of leucocytes and they called the toxin isolated leucotoxin. Caspari, applying the same principle for the tumor cells, arrived at the conclusion that the disintegrating cells liberate similar substances, which he calls necrohormones.

There are numerous methods of producing a stimulation of the lymphocytes, and of course, all these methods are in direct relation with the increase of the resistance of the organism as a whole. Nakahara succeeded in producing a stimulation of the lymphocytes in mice by injecting olive oil transperitoneally. Murphy and Sturm, and Nakahara increased the lymphocytosis by the action of the heat, and Aschenheim and Meyer, Clark, and Sonne, by the action of the sun's rays or concentrated light. Since Murphy and Morton first observed that an increase in the number of circulating lymphocytes in mice can be produced by the application of very small doses of roentgen rays of low penetration, a number of experiments and observations have been made on this subject by Thomas, Taylor and Witherbee, Russ and co-workers, Lacassagne and Samssonow, and especially by Murphy and Nakahara and their co-workers. These latter, in a series of experiments on mice, showed that irradiation is capable of producing: (1) a local lymphocytic infiltration around the irradiated tumor, and (2) an increase in the number of circulating lymphocytes, due to an increase in the proliferative activity of the lymphoid organs.

From this, the conclusion is derived that the lymphocyte is the most important factor in producing the so-called resistant state, and the effects of the roentgen rays depend in the first instance on the mobilization of the lymphocytes. Recently, Carrel brought another important contribution to the problem when he succeeded in stimulating the

growth of the fibroblasts *in vitro* by the presence of lymphocyte cultures, thus furnishing evidence that the connective tissue formation around the irradiated tumor is the direct result of the lymphocytic infiltration produced by the roentgen rays.

The establishment of the above facts, as we shall see, will greatly facilitate our task in interpreting phenomena observed during the roentgen treatment of the lesions of the lymphoid tissues, and will enable us to arrive at some definite conclusions with regard to the method of treatment to be used in the particular instances.⁵

In addition to Evans and Leucutia's conclusions that the foregoing work is of assistance in treating lesions of the lymphoid system, it can easily be seen that it has a direct bearing on the use of small frequent doses in the treatment of infections.