Effect of Irradiation on the Universal Reaction in Cancer*

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The universal serologic reaction (1, 2) is believed to be an immunologic indicator of tissue break-down. If this is true, the reaction should show changes resulting from the tissue injury incident to irradiation. That irradiation of animals is followed by changes in their universal reactions is indicated by experiments in progress in this laboratory. The determination whether patients undergoing irradiation show changes was suggested by Dr. Shields Warren of the Atomic Energy Commission. Preliminary studies of universal reactions before and after irradiation of cancer patients will be considered in this article.

Only such data are herein presented that are necessary for a brief introductory report. To determine fully the effect of irradiation on the universal reaction in cancer will require long-range observations of cancer patients undergoing varying degrees of irradiation, with universal reactions repeated at given intervals. However, the fact that the results appear to be of some clinical value suggested the desirability of presenting a report at this time.

The universal reaction.—The universal reaction is a serologic precipitation reaction to lipids based on different NaCl concentrations and different periods of incubation. The universal technic herein considered consists of seven quantitative set-ups. The technical steps of each set-up are similar to those employed in the performance of a quantitative Kahn test, with the exception of the use of different NaCl concentrations and incubation periods. The serum to be examined is first heated for 30 minutes at 56° C. The ratios of serum to diluent employed in each quantitative set-up are: 1:1, 1:2, 1:4, 1:8, 1:16, 1:64, and 1:256. In the first set-up, serial dilutions with serum are made with distilled water; in the second the serial dilutions of serum are made with 0.15 per cent NaCl solution; in the third with 0.6 per cent NaCl solution; in the fourth with 0.9 per cent; and in the fifth, sixth, and seventh set-ups the serial dilutions of serum are made with 1.2, 1.8, and 2.1 per cent NaCl solutions, respectively. Kahn antigen suspension is prepared in the usual manner and permitted to stand for 10 minutes before use. Each of the serial serum dilutions is then mixed with the suspension in a ratio of 6:1, employing 0.15-cc. amounts of the dilutions and 0.025-cc. amounts of the suspension. The mixtures of serum dilutions and suspensions are agitated for 3 minutes in a Kahn shaking machine and the precipitation results read immediately. The results are then further read after 4 and 24 hours' incubation at 5° C.

Table 1 presents an example of a single reading of the precipitation results of the seven quantitative set-ups. Chart 1 illustrates these readings graphically in the form of individual columns on the left side and in the form of a curve arrived at by interpolation on the right side. The cross-hatched area enclosed by the curve and the coordinates represents the zone of precipitation. In the charts in this and in the following article the precipitation results are presented in triplicate curves, comprising all three readings. The graphic presentation of individual columns in Chart 1 is given merely to facilitate the understanding of the relationship between the tabulated precipitation readings and the curves. For economy of space, the curves of Charts 2 and 3 of the universal reactions are presented in miniature form.

EXPERIMENTAL

The general plan of this study was to obtain blood specimens for universal reactions from cancer patients when they reported for irradiation to the Department of Roentgenology, University Hospital, and to submit these to the Serology Laboratory; then to obtain other blood specimens for universal reactions from the same patient about 2 or 3 months after they had received the irradiation therapy, depending on the time when they returned to the hospital for a check-up. In the data to be considered below, only two universal reactions per patient are presented, one

*This work has been supported by the Atomic Energy Commission, under Contract No. AT (11-1)-SS. Principal investigators: Reuben L. Kahn and Fred J. Hodges, University Hospital, University of Michigan, Ann Arbor, Mich.

Received for publication August 15, 1951.
obtained before and in some instances during irradiation, and the other after irradiation. In later reports it is planned to present data that are being collected on the relationship between irradiation and universal reactions, based on follow-up studies extending for some years.

The blood specimens obtained before and after irradiation were submitted to the laboratory as "unknowns," and, at the time of the performance of the universal technic, the laboratory staff had no knowledge of the clinical status of the patients. As indicated, the clinical data and universal results were obtained in different units of the University Hospital.

On classifying the universal reactions, it was observed that, following irradiation, certain cancer patients showed increased precipitation compared to the pre-irradiation reactions; others showed no increase, and a few showed a decrease. The question then arose whether a change or lack of change in the universal reactions had any clinical significance. The universal reactions of five cancer patients which showed increased precipitation are presented in Chart 2, together with the clinical histories. The reactions of five other cancer patients which showed no increase in precipitation are presented in Chart 3, with the clinical histories.

It should be pointed out that the universal reaction, based on the technic herein employed, is apparently incapable of showing serologic patterns of increased precipitation over the normal level in nonirradiated cancer patients. Studies of the universal reaction in cancer patients have been carried out in collaboration with the Department of Surgery of the University Hospital during the past 2 years, and, in the serologic examination of more than 300 cancer patients, no definite increase in precipitation over the normal level has been observed; but a tendency toward decreased precipitation has been noted in patients with metastasis. Hence, the increase in precipitation in the universal reaction following irradiation, shown in Chart 2, is interpreted to be the result of the irradiation.

Patient C.J. (Chart 2), with carcinoma of the cervix, was first examined for a universal reaction on August 10, 1950. The patient was given deep x-ray therapy and radium, and, on October 20, 1950, the universal reaction showed increased precipitation. On that date the patient manifested clinically a normal post-irradiation course. Actually, the patient continued to show improvement after that date, as is evident from the clinical history. But no attempt is made here to correlate the continued improvement with the increased precipitation in the universal reaction. The concern here is with the patient's condition on or about October 20, 1950, when the blood specimen for the post-irradiation universal reaction was taken.

Patient L.S., with carcinoma of the endometrium, was first examined for a universal reaction on August 31, 1950. The patient was given deep x-ray therapy and radium and, in addition, underwent a hysterectomy. In this patient the universal reaction showed increased precipitation on December 13, 1950, while the favorable clinical report was made more than 5 weeks later, on January 23, 1951. It is evident from the clinical history, however, that, on the date of the hysterectomy, no recognizable neoplasm could be found on microscopic examination. The improved condition of the patient was thus evident in November, and the increased precipitation in the universal reaction in December.

In patient H.H., with lymphoblastoma, Hodgkin's disease type, the date of increased precipitation in the universal reaction corresponded to the favorable clinical findings of regression in the cervical mass. This patient developed symptoms of abdominal disease 6 months later, and at that time would undoubtedly have shown another type of universal reaction. In the remaining two patients listed in Chart 2, the increase in precipitation in
### UNIVERSAL REACTIONS IN IRRADIATED CANCER

#### PRECIPITATION INCREASED

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Chief Complaint</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Radium</th>
<th>Univ. Reactions</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.J.</td>
<td>59</td>
<td>Vaginal bleeding, otherwise asymptomatic</td>
<td>Carcinoma of the cervix; stage III (League of Nations)</td>
<td>Deep x-ray therapy: 2,800 r to each of 4 fields 8-9-50 to 9-6-50</td>
<td>6,000 mg. hrs, 9-5-50</td>
<td>8-10-50 and 10-20-50</td>
<td>Radium reaction (necrotic membrane) on cervix 10-20-50; Pelvis otherwise unchanged; Vaginal apex almost healed (pelvis unchanged) 1-29-51; Vaginal apex healed (pelvis unchanged) 4-30-51; Normal post-irradiation course 10-20-50</td>
</tr>
<tr>
<td>L.S.</td>
<td>87</td>
<td>Vaginal bleeding</td>
<td>Carcinoma of the cervix; stage II (League of Nations)</td>
<td>Deep x-ray therapy: 2,925 r to each of 4 fields 8-9-50 to 9-6-50; Surgery: Hysterectomy 11-19-50; Microscopic examination showed no recognizable neoplasm</td>
<td>5,050.33 mg. hrs, 9-6-50</td>
<td>8-11-50 and 18-19-50</td>
<td>Normal post-irradiation course 1-29-51; No clinical evidence of neoplasm</td>
</tr>
<tr>
<td>H.H.</td>
<td>56</td>
<td>Mass in neck</td>
<td>Lymphoblastoma, Hodgkin’s Disease type</td>
<td>Deep x-ray therapy: 8,000 r to one cervical field directed over a large mass in the left side of the neck</td>
<td>4,900 mg. hrs, 8-24-50</td>
<td>8-9-50 and 10-23-50</td>
<td>Regression of cervical mass, asymptomatic 10-23-50; Symptoms of abdominal disease, therapy reinstated 4-23-51</td>
</tr>
<tr>
<td>E.C.</td>
<td>59</td>
<td>Vaginal bleeding</td>
<td>Carcinoma of the cervix</td>
<td>Deep x-ray therapy: 8,070 r to each of 8 fields 1-16-51, 8-19-51</td>
<td>4,900 mg. hrs, 8-24-50</td>
<td>1-17-51 and 8-9-51</td>
<td>Normal post-irradiation course 5-9-51</td>
</tr>
<tr>
<td>F.W.</td>
<td>50</td>
<td>Vaginal bleeding</td>
<td>Carcinoma of the cervix; stage II (League of Nations)</td>
<td>Deep x-ray therapy: 8,000 r to each of 4 fields 11-19-50 to 18-9-50</td>
<td>4,901 mg. hrs, 10-19-50</td>
<td>11-16-50 and 18-16-50</td>
<td>Normal post-irradiation course 1-29-51</td>
</tr>
</tbody>
</table>
Considerations of the serologic results.—Before considering the results, it will be well to touch upon several aspects of the universal reaction reported elsewhere (1, 2). All human beings and animals tested thus far have been found to show some precipitation in their universal reactions. These reactions are differentiable from one another by differences in precipitation patterns. Different normal individuals generally give precipitation patterns which, to a greater or lesser degree, differ quantitatively from one another, while a given normal individual commonly gives a constant precipitation pattern.

The behavior of the universal reaction in several diseases studied was found to be similar to that of a specific immunity reaction. Thus, in syphilis, malaria, and in early tuberculosis the universal reaction was found to show increased precipitation over the normal level and to revert to that level on recovery. In a given disease, precipitation is marked when the disease is in a moderately active state and is generally at a low level when the disease is in a very high state of activity. For example, while precipitation is often marked in early tuberculosis, it is at a low level in the far advanced and miliary forms of the disease. Similarly, precipitation is marked in moderately advanced lepromatous leprosy, but not in the far advanced form.

Increased precipitation in the universal reaction over the normal level has also been noted following the injection of various substances in rabbits (3, 4). The substances employed were both antigenic (horse serum and killed tubercle bacilli) and nonantigenic (tissue lipids and paraffin oil). The animal irradiation studies in progress have already been mentioned. These studies indicate that irradiation also causes an increase in precipitation in the universal reaction.

As a working hypothesis it is believed that the biologic mechanism of lipid antigen-antibody reactivity, manifested by the universal reaction, is essentially the same in health, in disease, upon injection of various substances, and following irradiation. A common factor associated with this mechanism apparently is tissue break-down, ranging from normal catabolism to marked tissue break-down in disease. Tissue break-down causes liberation of lipids from body cells. Some of these lipids undergo chemical changes which render them foreign to the body and antigenic. Autoantibodies, formed to these antigenic lipids, are then detected by the universal reaction.

Based upon these considerations, the results obtained in the present study are understandable. It might have been assumed that, since a given
UNIVERSAL REACTIONS IN IRRADIATED CANCER

PRECIPITATION DECREASED

JM 9-1-50

AS 6-1-50

JM 10-4-50

AS 11-9-50

PRECIPITATION UNCHANGED

JM 9-3-50

BMcN 10-26-50

JM 9-30-50

BMcN 12-7-50

CHART 3

CLINICAL HISTORIES

J.M. FEMALE Age 66
Diagnosis: Carcinoma of the ovary. Previous surgery and x-ray treatment; colostomy, small bowel obstruction on admission.
Treatment: Deep x-ray therapy; 800 r to each of 8 abdominal fields 8-11-50 to 8-8-50
Univ. reactions: 9-1-60 and 10-4-50
Progress: Down-hill course (considered terminal) 10-4-50
Autopsy 11-13-50; abdominal carcinomatosis

B.McN. MALE Age 60
Diagnosis: Recurrence of carcinoma of the epiglottis following amputation of the epiglottis 4-7-50, with cervical node metastasis
Treatment: Deep x-ray therapy: 3,775 r to left cervical field 10-15-50 to 11-14-50; 3,815 r to right cervical field
Univ. reactions: 10-10-50 and 11-13-50
Progress: No change as of 12-13-50; no evidence of neoplasm 5-11-51

J.M. MALE Age 70
Diagnosis: Renal neoplasm, left (right renal carcinoma removed 1944)
Treatment: Deep x-ray therapy: 5,000 r to each of 5 fields 8-4-50 to 8-11-50
Univ. reactions: 8-8-50 and 8-31-50
Progress: General condition of patient poor; no observation after 8-11-50

G.S. FEMALE Age 60
Diagnosis: Carcinoma of cervix; stage I (League of Nations)
Treatment: Deep x-ray therapy; 6,000 r to each of 4 pelvic fields 8-5-50 to 8-30-50
Radium: 8,000 mg. hrs. 8-31-50
Univ reactions: 8-8-50 and 8-31-50
Progress: No clinical evaluation possible as of 8-31-50
degree of irradiation is likely to produce the same degree of tissue injury in different patients, the lipids liberated and the antibodies produced in these patients would be such as to lead to universal reactions of similar intensity. Actually, because the behavior of the reaction is that of an immunity reaction, those irradiated patients who are going down-hill clinically could not be expected to show the same capacity for antibody production as those who are improving.

The increase in precipitation in the universal reaction, manifested by the irradiated cancer patients listed in Chart 2, indicates that the injury to the cancer tissue caused by the irradiation resulted in improvement of the patients sufficient to enable them to respond with increased antibody production to liberated lipids. The lack of increase in precipitation in the universal reaction, manifested by the irradiated cancer patients listed in Chart 3, indicates that the irradiation apparently failed to improve the patients sufficiently to enable them to respond with increased antibody production to the liberated lipids. A reasonable explanation for this inability to increase their antibody production is the general debility of the patients, due in most instances to metastasis. Needless to say, lack of increase in precipitation will also be noted when insufficient time is allowed for increased antibody production following irradiation, as in patient G.S. (Chart 3).

Superimposed disease or immunizing injections might affect the degree of precipitation in the universal reaction in irradiated cancer patients. It is conceivable that in a certain cancer patient the irradiation might be clinically successful, but, instead of increased precipitation in the universal reaction, no increase might be noted because of the patient's inability to increase the production of antibodies above the pre-irradiation level as a result of severe illness unrelated to cancer. However, an increase in precipitation in the universal reaction of a cancer patient following irradiation, even in the presence of superimposed disease or immunizing injections, might suggest a capacity to increase the production of antibodies. This capacity in turn would indicate improvement, since it apparently would be absent in metastasis.

It is evident that only by means of extensive and prolonged studies of the universal reaction in irradiated cancer patients, with repetition of the reaction every few months, will it be possible to determine the extent to which it may serve as an aid to the clinician in interpreting the results of irradiation therapy in cancer.

SUMMARY

Preliminary studies of universal reactions before and after irradiation of cancer patients led to the following results:

1. Patients whose universal reactions exhibited a rise in precipitation following irradiation were found to manifest clinically a normal post-irradiation course.

2. Patients whose universal reactions exhibited no rise or a decline in precipitation following irradiation were found to be in a very poor state clinically and did not manifest a normal post-irradiation course.

ACKNOWLEDGMENT

The authors wish to thank Miss Ellen Blue for technical assistance.

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Effect of Irradiation on the Universal Reaction in Cancer

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