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 5 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
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

PRECIPTITATION INCREASED

CHART 2

CLINICAL HISTORIES

C.J. **FEMALE** **AGE 59**
Chief complaint: Vaginal bleeding, otherwise asymptomatic
Diagnosis: Carcinoma of the cervix; stage III (League of Nations)
Treatment: Deep x-ray therapy: 2,800 r to each of 6 fields 8-9-50 to 9-1-50
Radium: 0,000 mg. hrs. 9-5-50
Univ. reactions: 8-10-50 and 10-20-50
Progress: 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

L.S. **FEMALE** **AGE 67**
Chief complaint: Vaginal bleeding
Diagnosis: Carcinoma of the endometrium
Treatment: Deep x-ray therapy: 2,882 r to each of 6 fields 8-9-50 to 9-1-50
Radium: 0,000 mg. hrs. 9-5-50
Surgery: hysterectomy 11-19-50; microscopic examination showed no recognizable neoplasm
Univ. reactions: 8-31-50 and 10-18-50
Progress: Normal post-irradiation course 1-29-51. No clinical evidence of neoplasm

H.H. **MALE** **AGE 66**
Chief complaint: Mass in neck
Diagnosis: Lymphoblastoma, Hodgkin's Disease type
Treatment: Deep x-ray therapy: 8,000 r to one cervical field directed over a large mass in the left side of the neck
Univ. reactions: 8-9-50 and 10-23-50
Progress: Regression of cervical mass, asymptomatic 10-23-50
Symptoms of abdominal disease, therapy reinstated 4-23-51

E.C. **FEMALE** **AGE 39**
Chief complaint: Vaginal bleeding
Diagnosis: Carcinoma of the cervix
Treatment: Deep x-ray therapy: 2,800 r to each of 6 fields 1-16-51, 8-19-51
Radium: 0,000 mg. hrs. 9-4-51
Univ. reactions: 1-17-51 and 3-9-51
Progress: Normal post-irradiation course 3-6-51

F.W. **FEMALE** **AGE 50**
Chief complaint: Carcinoma of the cervix; stage II (League of Nations)
Treatment: Deep x-ray therapy: 8,000 r to each of 4 fields 11-15-50 to 18-8-50
Radium: 0,001 mg. hrs. 18-18-50
Univ. reactions: 11-16-50 and 18-16-50
Progress: Normal post-irradiation course 1-29-51
the universal reaction also corresponded clinically to normal post-irradiation courses.

A different relationship between the universal reaction and the clinical post-irradiation course of cancer patients is noted in Chart 3. Patient J.M., with carcinoma of the ovary and with a number of complications, ran a down-hill course clinically in spite of the irradiation. The patient's universal reaction of September 1, 1950, showed reduced precipitation compared to the pre-irradiation reaction. In patients J.M. and B.McN., the clinical histories do not indicate a normal post-irradiation course. Patient J.M. was in an especially poor state, with a neo-

Precipitation following irradiation. In patients A.S. also showed reduced precipitation in the universal reaction. Although follow-up studies were not possible in this case, the fact that the carcinoma of the larynx was far advanced gives strong indication of the poor clinical condition of the patient. In the next three cancer patients listed in Chart 3, the universal reactions showed no changes in precipitation following irradiation. In patients J.M. and B.McN., the clinical histories do not indicate a normal post-irradiation course. Patient J.M. was in an especially poor state, with a neo-

plasm of the left kidney after the right one had been removed. Patient B.McN. had recurrence of carcinoma of the epiglottis with cervical node metastasis. It might have been expected that these two patients, like the two above, would show reduced precipitation in their universal reactions, in view of their poor clinical conditions. The answer might lie in the fact that the degree of precipitation in their pre-irradiation universal reactions was so reduced already as to have very nearly reached bottom, so to speak. Patient G.S. is of interest. The pre-irradiation reaction of this patient was obtained on August 8th and the post-irradiation reaction on August 31st. This is the shortest period between the pre- and the post-irradiation reactions reported in the present study. The irradiation was completed on August 31st, and the blood specimen for a universal reaction was obtained the same day, which may explain why no increase in precipitation was noted. This is the main reason the universal reaction of G.S. was included in this study—to indicate that a sufficient period following irradiation may be necessary before an increase in precipitation is manifested. It is evident from the serologic studies of the small group of irradiated cancer patients herewith presented that universal reactions of increased precipitation correspond clinically to normal post-irradiation courses, while universal reactions of decreased precipitation, or of no change in precipitation, correspond clinically to poor post-irradiation courses.

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. Auto-

antibodies, 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
CLINICAL HISTORIES

J.M.  FEMALE  AGE  48
Diagnosis: Carcinoma of the ovary. Previous surgery and x-ray treatment; small bowel obstruction on admission.
Treatment: Deep x-ray therapy: 800 r to each of 8 abdominal fields 8-11-40 to 9-11-50
Univ. reactions: 9-1-50 and 10-4-50
Progress: Downhill 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: 5,775 r to left cervical field 10-10-50 to 11-12-50; 5,850 r to right cervical field 10-10-50 to 11-12-50
Univ. reactions: 10-28-50 and 11-13-50
Progress: No change as of 12-13-50; no evidence of neoplasm 5-11-51

G.S.  FEMALE  AGE  20
Chief complaint: Vaginal bleeding
Diagnosis: Carcinoma of cervix; stage I (League of Nations)
Treatment: Deep x-ray therapy: 8,000 r to each of 4 pelvic fields 8-6-50 to 8-31-50
Radium: 6,000 mg. hrs. 8-31-50
Univ reactions: 8-6-50 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, mani-
ifested by the irradiated cancer patients listed in
Chart 3, indicates that the irradiation apparently
failed to improve the patients sufficiently to en-
able them to respond with increased antibody pro-
duction to the liberated lipids. A reasonable ex-
planation for this inability to increase their anti-
body production is the general debility of the
patients, due in most instances to metastasis.

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