THE EFFECT OF COMBINED RADIATION AND HEAT ON NEOPLASMS *

G. L. ROHDENBURG, M.D., AND FREDERICK PRIME, M.D.
NEW YORK

As a result of animal experimentation and clinical experience, it has become evident that extremely large doses of radiation are necessary to kill neoplastic cells which are located at any considerable distance from the surface of the body. Such dosage is often productive of untoward effects on contiguous and intervening normal tissues, may induce a serious general reaction, and has been known occasionally to cause death. If the lethal action of radiant energy on the tumor cell could be supplemented by that of some other nocive agent which does not increase the general or local damage to the body, it might be possible to extend the field of application of radiation to tumors at present inaccessible.

The fact that, in many instances, spontaneous recession in human tumors was observed to follow a period of fever led us, in 1916, to try the effect of raising the temperature of animals with implanted tumors. This experiment failed because mice and rats rapidly succumb to moderate degrees of heat.

The experiments subsequently recorded by Bovie,[1] in which he showed that proteins exposed to ultraviolet light coagulated at a much lower temperature than did untreated protein, again suggested the idea that this heat might be applied clinically and serve as a method of increasing the therapeutic range of radiation. It was, therefore, to determine the value and limitations of a combination of radiation and heat as applied to the treatment of cancer that the experiments here recorded were planned.

The use of a combination of the two physical agents, radiation and heat, is not entirely novel. The effect of low degrees of heat alone on transplantable animal tumors has been studied by Jensen,[2] Loeb,[3] Clowes[4] and R. A. Lambert,[5] and, more recently, in this

* From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director.

1. Bovie, W. T.: J. Cancer Research **5**:88 (Jan.) 1920.

2. Jensen: Centralbl. f. Bakteriol., I Abt. Orig. **34**:129, 1903.

3. Loeb: J. M. Research, N. S. **3**:62, 1902; Virchows Arch. f. path. Anat. **162**:345, 1903.

4. Clowes: Brit. M. J. **2**:1549, 1906.

5. Lambert, R. A.: Demonstration of the Greater Susceptibility to Heat of Sarcoma Cells as Compared with Actively Proliferating Connective-Tissue Cells, J. A. M. A. **59**:2147 (Dec. 14) 1912.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

laboratory by Stevenson,[6] and it has been shown that neoplastic cells are relatively easily killed by this agent, although cancer cells are no more susceptible than are rapidly growing normal cells. The relationship existing between the degree of heat and the length of time that it was applied has not been thoroughly investigated, though Stevenson's experiments were directed toward this question. The actual cautery was used as a therapeutic agent in cancer by the ancients, and, more recently its use has been revived in modified form by Percy[7] and New.[8] The combination of high degrees of heat and radiation was first applied by de Keating-Hart,[9] and in this instance the heat was produced by the high frequency electrical current.

Fulguration and diathermy were also used, either singly or in combination with radiation, by Iredell and Turner,[10] Harner,[11] and Beebe and Van Alstyne.[12] All these authors applied the method in a manner widely different from that used in the experiments described herewith. Schmidt,[13] however, advanced the theory that heat sensitizes the tissues to radiation and stated that this sensitization can be accomplished by diathermy. He announced that he would publish his clinical data later, but we have not been able to find any subsequent article by this author dealing with his experience.

Theilhaber[14] described a method very similar to the one we have employed. In his experience greater lethal effect was produced when tissues were radiated first and heated subsequently. He also drew attention to the fact that normal as well as malignant tissues were sensitized. Theilhaber used large electrodes and an amperage which approximated that used by us, but did not apply the current for so long a period of time as we did. He described several treated cases but gave no detailed data.

The present investigations may be considered under several headings: (*a*) the effect of heat upon fragments of transplantable tumor in vitro; (*b*) the effect of a combination of radiation and heat upon

---

6. Stevenson, H. N.: J. Cancer Research **4**:54 (Jan.) 1919.

7. Percy, J. F.: Surg., Gynec. & Obst. **22**:77 (Jan.) 1916.

8. New, G. B.: Treatment of Malignant Tumors of the Antrum, J. A. M. A. **74**:1296 (May 8) 1920.

9. De Keating-Hart: La fulguration et ses résultats dans le traitement du cancer, d'après une statistique personnelle de 247 cas, Paris, 1909.

10. Iredell, C. E., and Turner, P.: Proc. Roy. Soc. Med. (Sect. Electrotherap.) **12**:23 (June) 1919.

11. Harner: Brit. M. J. **2**:1017, 1914.

12. Beebe and Van Alstyne: Surg., Gynec. & Obst. **18**:438, 1914.

13. Schmidt: Fortschr. a. d. Geb. d. Röntgenstrahlen **14**:135, 1909.

14. Theilhaber, Adolf: Die Entstehung und Behandlung der Karzinome, Berlin, S. Karger, 1914.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

fragments of transplantable tumor in vitro; (*c*) the effect of heat upon spontaneous tumors in vivo, and (*d*) the effect of a combination of heat and radiation upon spontaneous tumors in vivo.

THE EFFECT OF HEAT UPON FRAGMENTS OF TRANSPLANTABLE TUMOR IN VITRO

Although the recorded experiments in which the action of heat has been studied are extensive, there is still some confusion as to the death point of the neoplastic cell. This confusion is due in part to a lack of appreciation of the correlation between the degree of

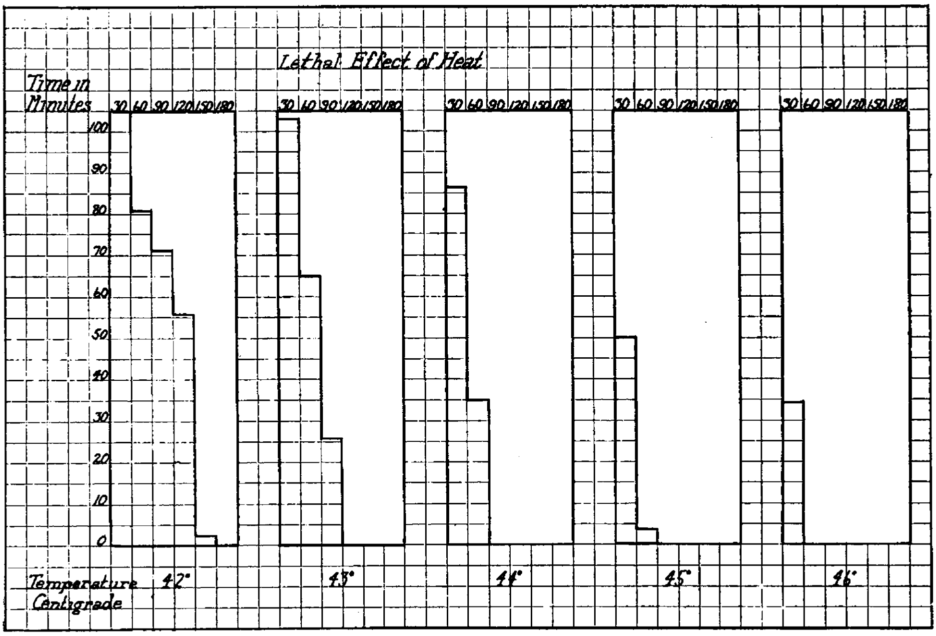

Chart 1.—Lethal effect of heat on tumor cells.

temperature used and the period for which heat is applied. Another factor influencing the results so far published is the biology of the tumors employed. In determining the lethal effect of any agent upon a tumor cell, it is essential that a tumor be used which does not undergo spontaneous recession after inoculation in any considerable percentage of cases. The Crocker mouse sarcoma 180 meets this requirement, since observations extending over five years and comprising about 5,000 tumors show an average of 98 per cent. of "takes" with less than 1 per cent. of spontaneous recessions.[15]

15. Prime: Paper read before the American Association for Cancer Research, April, 1920.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

The technic employed in the first series of experiments was as follows: All manipulations were performed under sterile conditions. A tumor was cut into small fragments for inoculation (0.002 to 0.003 gm.). These fragments were placed in test tubes containing Ringer's solution which had been previously raised to the temperature of the experiment. The test tubes with their contents were then placed in a water bath, and kept at the given temperature for the time period specified. At the expiration of this period the Ringer's solution was poured off and cold Ringer's solution substituted to check further action of the heat. As controls, similar fragments of the same tumor were placed in cold Ringer's solution for the period of time that the

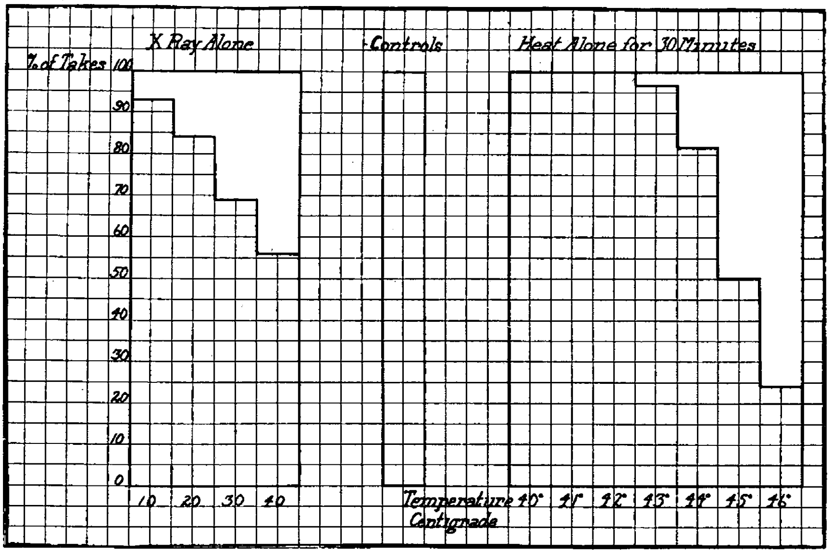

Chart 2.—Effect of combined heat and radiation on fragments of transplantable tumor in vitro.

other fragments were exposed to heat. Both sets were then inoculated subcutaneously into mice in the usual fashion, a trocar and needle being used. In this manner, many series of twelve animals each were inoculated, the grand total, including controls, being 2,684 animals. The temperatures to which the tumors were exposed were 42, 43, 44, 45 and 46 C., and the time periods with each fixed temperature were 30, 60, 90, 120, 150 and 180 minutes. The animals were kept under observation for five weeks after inoculation, when the percentage of "takes" was determined. The data are graphically presented in Chart 1.

With a temperature of 42 C., the first lethal effect is evident after sixty minutes' exposure and from this point on there is a rapid increase in the lethal effect until at the 180 minute period it attains the maximum

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

of 100 per cent. With temperatures higher than 42 C., the lethal effect is in evidence sooner and attains its maximum with shorter periods of exposure until at 46 C. a thirty minute exposure is lethal in more than 60 per cent. of cases.

THE EFFECT OF COMBINED HEAT AND RADIATION ON FRAGMENTS OF TRANSPLANTABLE TUMOR IN VITRO

Having determined the lethal point for the Crocker mouse sarcoma 180 with different degrees of heat at different time intervals, and having the advantage of the results of the previous work of Wood and Prime,[16] who, using the same tumor strain, determined the lethal effect of radiation, we next employed a combination of the two agents, each in sublethal doses.

The technical steps in the experiments in this series were similar to those previously described. The heat exposures were made as previously stated, except that in combining the two physical agents, exposures were made only at 42, 43 and 44 C. for the fixed period of thirty minutes. This time interval represented the threshold of lethal effect at each of these temperatures.

The tumor to be exposed to radiation was cut into small fragments as before, and the fragments were placed in glass dishes with enough cold Ringer's solution to keep them moist, and were covered with a sterile cover glass. The radiation dose was 85,000 volts, 5 milliamperes, with a 3 mm. aluminum filter at a distance of 23 cm. for 10, 20, 30 and 40 minutes.

In these experiments, we again used repeated series of twelve animals each, the grand total being 3,248 animals. The series were as follows: (*a*) animals inoculated with untreated portions of the tumor; (*b*) animals inoculated with fragments treated with heat alone; (*c*) animals inoculated with fragments treated with roentgen ray alone; (*d*) animals inoculated with fragments treated with radiation first and heat directly afterward; (*e*) animals inoculated with fragments treated with heat first and radiation directly afterward. As before, the animals were observed for five weeks after inoculation and the percentage of "takes" was then determined. The data are graphically presented in Charts 2 and 3.

The untreated controls showed 100 per cent. "takes," the animals inoculated with fragments exposed to one erythema dose showed 93 per cent. "takes" and those inoculated with fragments exposed to three erythema doses, 68 per cent. The animals inoculated with frag-

16. Wood, F. C., and Prime, Frederick: Ann. Surg. **62**:751, 1915; Lethal Dose of Roentgen Ray for Cancer Cells, J. A. M. A. **74**:308 (Jan. 31) 1920.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

ments treated solely with heat showed 82 per cent. "takes" when the exposure had been to 44 C., and 100 per cent. when the exposure had been to 42 C.

When both heat and radiation are applied in sublethal dose, and it makes but little difference which is applied first, there is a marked lethal effect. Thus, while a temperature of 42 C. for a period of thirty minutes applied after one erythema dose has a lethal effect of but 10 per cent., and when the order of application of the agents is reversed no lethal effect is noted, a temperature only one degree higher produces a lethal effect of 76 per cent. in one instance and 91 per cent.

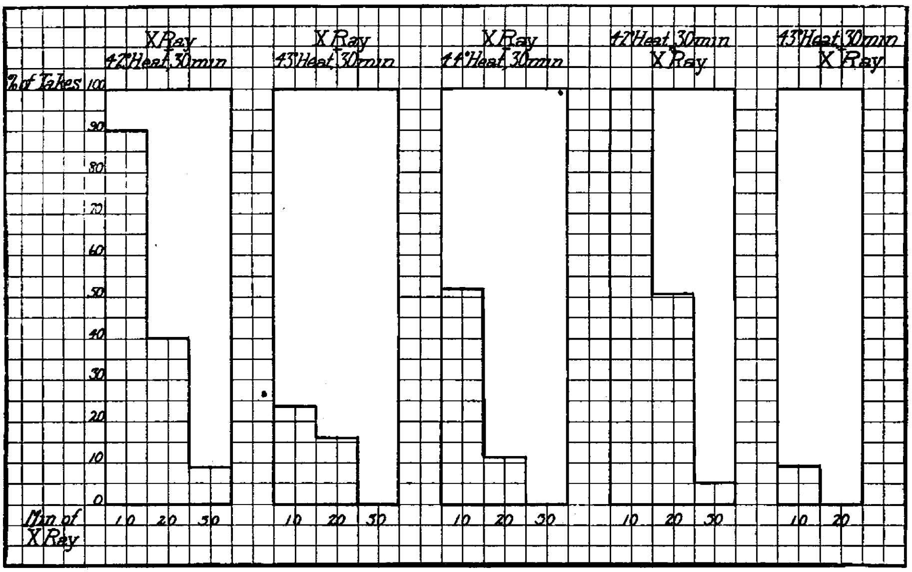

Chart 3.—Effect of combined heat and radiation on fragments of transplantable tumor in vitro.

in the other. The lethal effect of radiation combined with heat is not so marked at 44 C. as at the lower temperature of 43 C. This we have interpreted as an evidence of stimulation comparable to the stimulation which occurs with certain sublethal doses of radiation. The maximum lethal effect of 100 per cent. is obtained with three erythema doses and thirty minutes' exposure to 43 C., the radiation being applied first, or with two erythema doses and thirty minutes' exposure to 43 C., the heat being applied first. The slight difference is probably of no significance. According to the results obtained by Wood and Prime, five erythema doses alone are required to kill the cells of mouse sarcoma 180; and our previously described experiment with the

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

same tumor strain shows that 120 minutes' heating at 43 C. is required to kill. The combination of a given sublethal dose of the two agents, therefore, produces the same effect as four times the dose of heat when used alone, and as five times the dose of radiation when used alone.

THE EFFECT OF HEAT UPON TUMORS IN VIVO

Since the results of biologic experiments in vivo often are different from those of the same experiments in vitro, these observations were repeated on tumors in the animal body. For this reason in the later experiments, the tumors were heated by diathermy, a term applied to an alternating current of high frequency used so as to create heat in the tissues through which it passes. The degree of heat obtained,

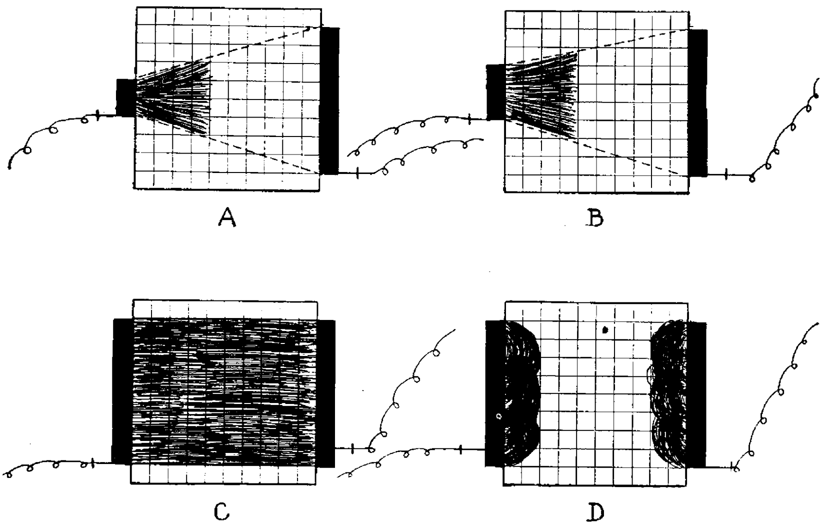

Chart 4.—Effect of electrode shape and current strength on intervening tissues: *A,* 10 ma., ten minutes; *B,* 100 ma., four minutes; *C,* 10 ma., ten minutes; *D,* 100 ma., four minutes. Strong current for a short time gives a superficial action (*B, D*). Weak current for a long period gives deeper action (*A, C*). If both electrodes are of the same area and the current is weak, the heated zone is cylindric (*C*). If one electrode is small or the current is strong, the heated zone is localized about the electrode (*B, D*).

and, hence, the physical changes which occur in the tissues are dependent on two conditions: (*a*) amperage and (*b*) shape and area of the electrode. By varying these two, all effects from a slight increase in temperature to charring of tissues are obtainable.

It was the aim in combining the two agents, radiation and heat, to produce relatively low degrees of temperature, and to continue them over relatively long periods, and it is in these two points that

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

the method employed differs from all others which have been recorded. Thus, a recent study of this subject [17] is based upon the use of 3 amperes of current for fifteen seconds with very small electrodes, and the conclusion is reached that the method is valueless. To anticipate, in order to indicate the difference between the method used in the present experiments and those in the work just referred to, it may be stated that we have employed 40 milliamperes for a period of twenty minutes with relatively large electrodes. The previous worker reported a typical burn reaction, while the tissues we have treated show no such changes. The temperatures we have employed are also very much lower than those used in the Percy or in any other cauterization or fulguration methods which have been advocated.

As has been stated before, the degree and type of effect of the heat generated by the high frequency current is dependent upon the shape of the electrode. Chart 4 illustrates the points which are of importance. If the electrodes are of unequal size, as in *A*, and the current weak, there will develop a zone of reaction penetrating for a considerable distance into the tissues but attaining its maximum at the small electrode. On the other hand, if the current is increased in strength, the effect is directly localized about the small electrode, as in *B*. If the electrode is of equal size and a weak current is employed, as in *C*, there is a cylindric area of action between the two electrodes, while if the current is strong there is a marked action about each electrode, but none in the depths of the tissues, as in *D*.

While the facts just stated are common knowledge, a search of the literature revealed no data on the amount of current necessary to produce a given rise in temperature. In order to determine this, diathermy was applied to various thicknesses of bone-free meat. The initial temperature of the meat before the application of diathermy was in each instance 10 C. and the given amperage was allowed to flow for a period of twenty minutes. A thermometer was placed in the tissue midway between the electrodes, and the temperature was noted every three minutes. The amperage is based on the square area of one electrode, and both electrodes were of the same shape and size.

Chart 5 presents a curve constructed on the data thus obtained, and while it is far from mathematically accurate, it is close enough for practical purposes. With an electrode with a surface area of 2.5 by 2.5 cm. and with 10 milliamperes, the increase in temperature

17. Stephan, Erich: Histologische Untersuchungen über die Wirkung der Thermopenetration auf normale Gewebe und Carcinom, Beitr. z. klin. Chir. **77**:382, 1912.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

produced by twenty minutes' application of current in varying thicknesses of tissue is as shown by the curve. If electrodes of twice this size are used, then the heat produced is one-half that recorded in the chart; and if living instead of dead tissues are used, the rise in temperature is approximately double that indicated on the chart. Why this is so we do not know. The increase of temperature in dead tissue for the first ten minutes of current flow is rather slow, but for the second ten minutes is more rapid; and while a continuation of

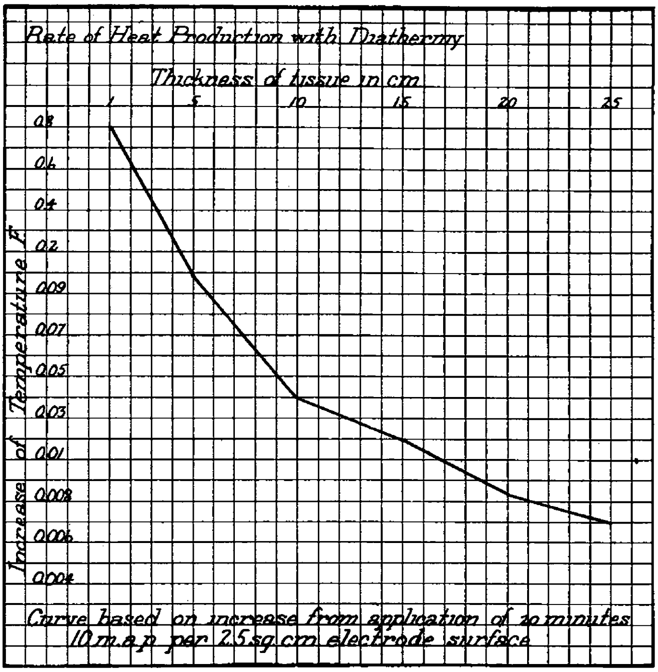

Chart 5.—Amount of current necessary to produce a given rise in temperature.

the same amount of current for more than twenty minutes gradually increases the temperature, this increase is extremely slow, and for practical purposes can be disregarded.

In applying the current to human beings the procedure is as follows: Electrodes of equal size and the same shape are cut from block tin. Gauze compresses, four or five folds thick, are moistened with water and applied to the skin, the compresses being made large enough to allow of a 4 cm. margin outside the electrode. Sparking due to imperfect contact of the electrode or to electrode connections with the skin must be avoided, for sparking is painful and produces burns.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

The amperage used is roughly fixed by determining in centimeters the square area of one electrode, dividing this by 6 (the square area of the electrode used in Chart 5), dividing the result by 2 (if the tissues are living), and multiplying the result thus obtained by 10 (the amperage used in the experiment on which Chart 5 is based). The amperage may, however, be more easily regulated by the sensation of the patient. Sparking being obviated, the amperage is increased until the patient states that the degree of heat is uncomfortable; the amperage is then decreased until the patient feels perfectly comfortable with the degree of heat that is being produced. The treatment is timed from twenty minutes after the current is turned on, so that, the average treatment being from thirty to forty minutes, the total exposure is approximately one hour. Our experiments have shown that low degrees of heat (41 C.) produce the same results as high degrees (46 C.), but to be effective the lower temperature must be applied for longer periods. This should be borne in mind when treatments are given.

For the purposes of histologic study of the changes in the tissues, a series of transplantable rat sarcomas and carcinomas were treated with diathermy (exposure twenty minutes); amperage, 40 milliamperes; area of electrode, 8 sq. cm.; depth of tissue, 5 cm. Some of the animals received but one treatment, and were killed at intervals ranging from twenty-four hours to one week after treatment; others received two, three and four treatments at two-day intervals, and were killed at intervals of from twenty-four hours to one week after the last treatment.

The histologic changes observed occurred in this sequence. Twenty-four hours after the treatment there was an intense congestion of all the small blood vessels of the tumor, most of them being from five to six times their normal diameter. This congestion was so intense as to give rise to a deep red color throughout the tumor; this occurred irrespective of whether the animal had had one or more treatments, and was demonstrable up to twenty-four hours after the last treatment. About three days after treatment, the cell outlines became obscure, though the nuclei still preserved their outline and staining qualities. Next the cytoplasm became decidedly acidophil, the tissues took the stains poorly and there was an evident karyorrhexis. About this period, some of the blood vessels became thrombosed, and vacuolation occurred in some of the cells, the connective tissue framework of the tumor standing out markedly owing to the degeneration of the parenchyma. At still later periods (three and six days) areas of liquefaction or massive coagulation necrosis were in evidence; and at the seventh day, replacement fibrosis began to be obvious arising from the

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

intact blood vessels at the periphery of the tumor or from the surrounding healthy tissue. Absorption of the necrotic material was extremely slow. It is interesting to note that while the untreated tumors showed an average of twenty mitotic figures to the field of a 12 mm. objective, a tumor treated but once showed no mitotic figures in 180 fields, twenty-four hours after treatment. Exposures

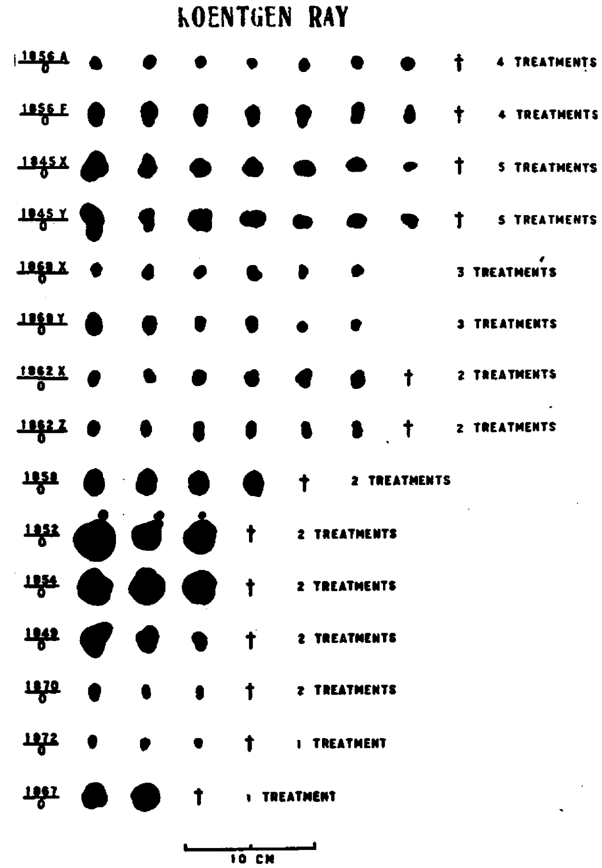

Chart 6.—Effect of combined heat and radiation on spontaneous tumors in vivo.

made at intervals more frequent than once in seven days did not increase the intensity of the reaction. Evidently, the damage done with one treatment cannot be duplicated until the neoplasm has had a chance to recuperate to some degree. There were no changes in the organs of the exposed animals which could be attributed to the treatment or to the absorption of dead material.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

EFFECT OF COMBINED HEAT AND RADIATION ON SPONTANEOUS TUMORS IN VIVO

For the purpose of this investigation, spontaneous tumors in mice of the "Lathrop" stock were used. The animals of this breed are particularly prone to develop tumors of the breast and all those treated originated in that locality. Some of the tumors were treated with

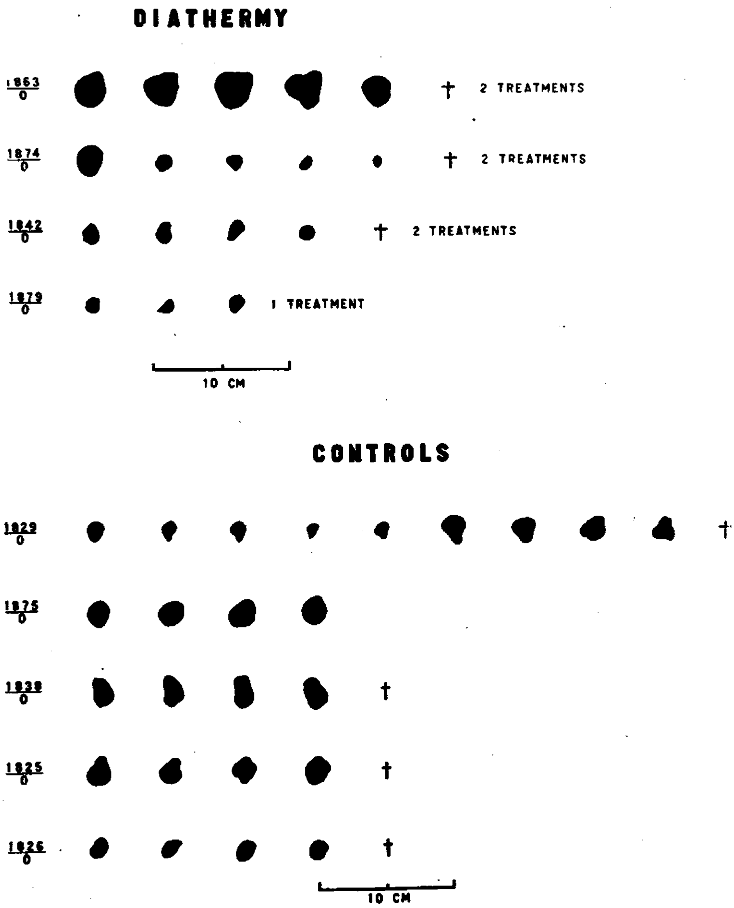

Chart 7.—Effect of combined heat and radiation on spontaneous tumors in vivo.

radiation alone, others with diathermy alone, and still others with a combination of the two agents. Radiation was given the tumor once in from seven to ten days, the distance being 23 cm. from the neoplasm, the rays filtered by 3 mm. aluminum with a voltage of 85,000 and 5 milliamperes through the tube for a period of twenty minutes.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

All parts of the animal except the tumor under treatment were carefully screened by heavy lead. Diathermy was given through a 2.5 cm. square electrode for a period of twenty minutes with 40 milliamperes once in seven or ten days. When radiation and heat were both applied it was done in some instances on the same day, in other instances at twenty-four hour intervals; sometimes heat was applied first, while at other times radiation was used first. The interval between successive combination treatments was from seven to ten days.

ROENTGEN RAY AND DIATHERMY

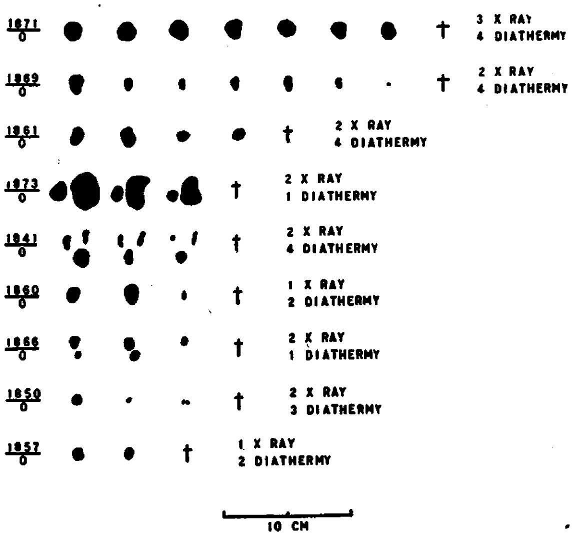

Chart 8.—Effect of combined heat and radiation on spontaneous tumors in vivo.

The results obtained are graphically shown in Charts 6, 7 and 8. The first column in each chart indicates the size of the tumor on commencing treatment, the other columns indicate the size of the tumor at subsequent weekly intervals. Tumors treated with diathermy or radiation alone show but little inhibition or recession in growth when compared to tumors treated by a combination of both of these agents.

CONCLUSIONS

Low degrees of heat applied for varying periods of time have a lethal action on neoplastic cells in vitro and this lethal action with proper dosage is effective in 100 per cent. of cases. Histologic examination of tumors which have been treated by diathermy reveals cellular changes similar to those observed in tumors exposed to radiation.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015

Wood and Prime have shown that any tumor may be killed by a sufficient dosage of either radium or roentgen ray; but that in many instances the patient will not survive the dosage necessary to bring about the death of all the cells of an internal, highly malignant carcinoma or sarcoma. Our experiments demonstrate that by combining radiation with an agent not so destructive to the organism the field of usefulness of radiotherapeutic measures may be extended.

The results obtained in the animal experiments show that the therapeutic range of radiation can be considerably increased.

While the principles worked out in the animal experiments here recorded are already being applied in the treatment of cases of neoplasia in human beings, the technical development of the method and the evaluation of the final results will require long and careful observation of the patients before its applicability can be demonstrated.

Downloaded From: http://archsurg.jamanetwork.com/ by a New York University User on 05/21/2015