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RADIATION THERAPY WITH HIGH-ENERGY ELECTRONS USING PENCIL BEAM SCANNING*

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In 1934 Brasch and Lange[1] reported on the use of what they termed "fast cathode rays" as a method of therapy. This apparently is the first paper dealing with the direct use of an electron beam as a therapeutic agent other than electrons from radioactive substances. The authors seem to have been quite in agreement with those who have considered this modality more recently. They cite as advantages: (1) well-defined range; (2) ability to give off more energy at the depth than on the surface; (3) high biologic activity; and (4) magnetic directability. While they were talking about electrons with only superficial penetrability, they did produce epilation without superficial radiation effect using electrons ranging from 0.7 mev. to 2 mev. No pigmentation was noted. They also found that the effects of overdose were similar to those of roentgen radiation.

REVIEW OF LITERATURE

Trump and his co-workers[20] described the therapeutic possibilities of electrons in their communication on the Van de Graaff electrostatic generator in 1940. This was, however, little improvement on the energy level of the original suggestion, although the generator was more elegant. Some clinical experience was presented, using what would now be termed "low energy electrons," by Trump *et al.*[19] in 1953. There had been earlier reports from Europe of the use of electrons ranging from 1 to 6 mev.[1,4,5,9,16]

The first mention of the use of high energy electron beam therapy was by Haas *et al.*[7] which appeared in 1954. These authors pointed out the advantages which had previously been described and also stated that the skin reaction did not differ essentially from that experienced with other radiations. This paper dealt with electrons from a 22 mev. betatron. There have been a number of other reports in the literature. Uhlmann[22] described the sharp cut-off in the mucositis produced in the process of

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treating a tongue lesion through a single portal. He also described mild skin reactions which cleared quite rapidly. In addition, he showed some of the advantages in treating deep-seated tumors by means of opposing portals. Lochman[11] described the reactions obtained with a 19 mev. beam of electrons and mentioned that the biologic effectiveness is roughly two-thirds of the effectiveness of ordinary roentgen rays of 2 mm. Cu half value layer quality. As a consequence, the skin and tumor doses administered to these patients were considerably higher than those given to most of the other reported patients. He concluded that at this energy level there are important advantages in the use of electrons for treatment of subsurface and unilateral head and neck malignancies. Uhlmann and Ovadia[21,22] have used higher energy electrons, 28 to 33 mev., for the treatment of pulmonary and esophageal lesions with promising early results.

Gale and Innes[4] have presented some very interesting dose distributions where mixed roentgen-ray beams and electrons are produced simultaneously by the same machine, using specially designed targets. They showed that this produces a flat beam and that the volume dose is considerably lowered. Chu and her co-workers[3] have used electron beams of varying energy for the management of both inoperable and locally recurrent carcinoma of the breast with what is described as good palliative results in a high percentage of patients. In only 1 of 70 patients was there evidence of radiation pneumonitis and skin reactions rarely progressed to small areas of moist desquamation, although the tumor doses were in the order of 6,000 rads to most of the areas treated. In addition, they were able to retreat several patients who had had prior roentgen therapy.

Ovadia and McAllister,[12] who work with Uhlmann, have described the use of a grid in electron therapy in order to protect the skin and normal tissue overlying tumors. The need for this is somewhat surprising in view of Uhlmann's previously quoted assertions which indicate minimal skin reactions. Ovadia and McAllister state that the skin reactions observed normally do not limit the treatment but may be a source of discomfort to the patient.

Veraguth[23] has described clinical experiments using electrons from 10 to 30 mev. His report concerns 200 patients with a wide range of malignancies, some of which had been previously treated by roentgen rays. He emphasizes the advantages of electrons: the uniform dose, sparing of sensitive tissues near tumors, reduced bone absorption and skin sparing. He points out that the mucosal reaction differs but little from conventional treatment but has observed a greater variation in time and intensity of reactions requiring closer observation of patients in order to judge response.

Zatz, von Essen and Kaplan[24] have used electrons from 10 to 40 mev. at Stanford University. They state that while the electron beam has very little skin-sparing effect compared to megavoltage roentgen rays, there is less skin reaction than with comparable doses of 200 kv. peak roentgen rays. Skin doses of 5,700 rads regularly produced severe dry reactions and usually wet reactions in large portions of the field but the reactions were less for small fields. They agree with other observers that the mucosal reactions are similar to those produced by equal doses of roentgen rays both in time of appearance and intensity. While their patients were treated at a higher weekly dose rate and a fractionation schedule of 3 treatments per week rather than 5, they do not feel that this is an adequate explanation for the increased skin effect. More recently, Perry *et al.*[13] have described in detail the methods of planning treatments for head and neck malignancies, using a range of 6 to 24 mev. Smedal and his co-workers[18] have reported good results in 522 patients with a variety of superficial lesions who were treated with electrons of relatively low energy, 1 to 4 mev.

EQUIPMENT AND PHYSICAL CHARACTERISTICS

Space does not permit detailed discussion of the physical applications and dosimetry of electron beam therapy. This material has been adequately presented in the articles quoted above, as well as in many others. Only a brief description of the equipment will be given and some of the unusual applications which are possible will be mentioned. The device which has been used in these studies is the linear accelerator and pencil beam scanning system of the Argonne Cancer Research Hospital of The University of Chicago.[14] The accelerator is of the traveling wave type and is powered by two klystrons in cascade (Fig. 1).

Energy control of the accelerated electron beam is obtained by setting the proper combination of radiofrequency power level of the klystrons and of phase of the electrons with respect to the radiofrequency wave in the second section of the wave guide. In this unit the electron energy is readily variable from 5 to 50 mev.

On leaving the accelerator, the electrons enter the unique pencil beam deflecting and scanning system[16] (Fig. 2). The scanning device directs the electron beam, which is approximately 0.5 cm. in diameter, over the tumor area of a patient. The beam is guided by means of magnetic fields and is capable of scanning arbitrary field sizes and shapes up to 20×20 cm. under one treatment method (Fig., 3 *A* and *B*, and 4). It can also be used to carry out convergent beam therapy over an arc up to 360°, with a width up to 20 cm. (Fig. 5 and 6). The beam is a pulsed beam with a repetition rate of 60 per second and a length of 1.2 microseconds. The patient area is elevated and a Siemens treatment cot is used (Fig. 7).

There are two quantities of the electron beam that need careful calibration to ensure proper patient dosimetry: (1) the energy of that portion of the beam which reaches the patient. The collimator de-

FIG. 1. The 5 to 50 mev. electron linear accelerator of the Argonne Cancer Research Hospital. Three klystron stations are shown, one of them a spare. The accelerator tube proper is contained in the protective housing shown on the left side of the picture. (Photograph courtesy of High Voltage Engineering Corporation, Burlington, Massachusetts.)

limits the electron energy to a band of ±½ per cent of the present energy. The energy of the beam is determined by magnetic deflection techniques; and (2) the intensity of the beam is established from a knowledge of the area covered by the beam per unit time and the absolute value of the electron current. The electron current itself is measured by means of a Faraday cage based on the design of Rozenfeld.[14]

The absorbed dose is determined on an absolute basis by making use of the energy and current intensity as well as the collision energy loss formulation of Sternheimer. This work on absorbed dose determination has been reported previously.[21]

The beam intensity is continuously monitored by means of a transmission ion chamber and the results are recorded (Fig. 7).

The very high dose rate of this system must be emphasized. If a typical cell of approximately 20 microns in diameter near the surface of a field which is receiving 300 rads in a single treatment is considered, it can be calculated that the cell receives its dose of 300 rads in 27 pulses of approximately 1 microsecond duration. The total time to deliver these 27 pulses at 60 pulses per second is 0.45 second, and the average

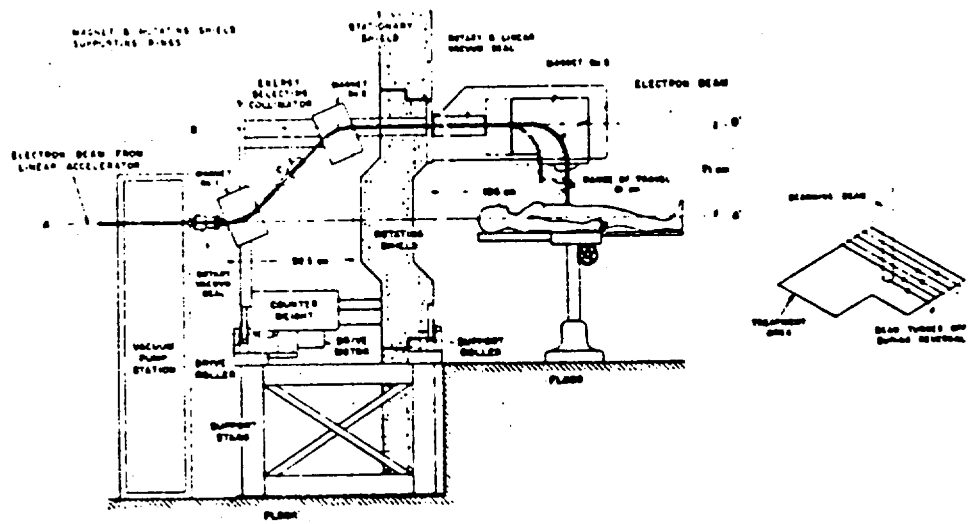

FIG. 2. Schematic drawing of pencil beam deflecting and scanning unit showing arrangement of magnet system, counter weight, rotating shield, treatment cot and patient. The electron beam is contained within a vacuum chamber not shown in this sketch. Inset on right illustrates scanning over a single portal.

dose per pulse is 11 rads. The dose rate averaged over the 1 microsecond pulse is then 11×10^6 rads per second; but, in addition, the pulse is further modulated by the accelerating radiowave so that 2,856 bunches or groups of electrons arrive during each 1 microsecond pulse. The duration of each bunch of electrons is not known accurately with the sharp energy collimation used; it cannot be appreciably greater than 1/[illegible]th of the inter-bunch interval and it may easily be as short as 1/[illegible]th of the interval. The pulse average dose rate must be multiplied by the reciprocal of these factors to obtain the instantaneous dose rate. Therefore, the dose is delivered in pulses of about

 FIG. 3. Scan pattern obtained by means of rotation and linear movement of magnet #3. (A) Scan spacing at 1.0 cm.; (B) scan spacing at 0.5 cm.

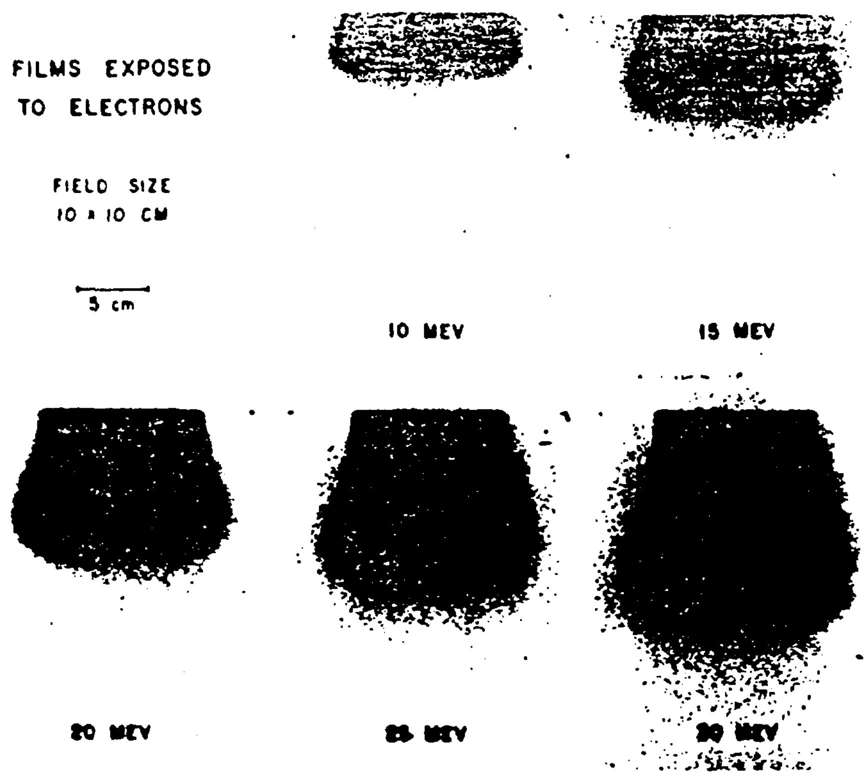

FIG. 4. Films, located within a phantom, exposed to electron beams of various energies.

0.004 rad each, with a dose rate of 200 to 500 times 10^6 rads per second. All of the other systems mentioned above use foil scattering and, while the beams are pulsed, the dose rate is much lower than in the case of the pencil scanning beam. There is a possibility that our high dose rate may play a part in the very limited skin reactions to be described later.

CLINICAL APPLICATION

Before undertaking patient treatment, LD_{50} curves in mice were run with both high energy electrons and cobalt 60 gamma rays. The relative biologic effectiveness (RBE) determined from these runs was 1.00 ± 0.07 where the 0.07 represents the 19/20 confidence limit determination for the "potency ratio."

Since our first patient was treated on June 16, 19[illegible], it is obvious that this presentation cannot deal with results of treatment in terms of cured disease. We have proceeded very slowly since we felt that we were dealing with an almost entirely new modality. Ninety-seven patients have been treated up to the present time. Fifty-one had malignancies of the head and neck, 8 had intrathoracic tumors, 5 had mycosis fungoides, 1 had an extensive recurrent squamous cell carcinoma of the skin of the thorax, 4 had carcinoma of the urinary bladder, 3 had benign lesions, and the remaining 25 had a variety of lesions treated on an experimental basis, most of them for palliation only. Thirty patients received tumor doses of 6,000 rads or better through single portals, 15 had lower doses aimed at cure, either because of tumor sensitivity or because irradiation was being used in combination with an experimental drug, and 42 patients received only palliative doses of

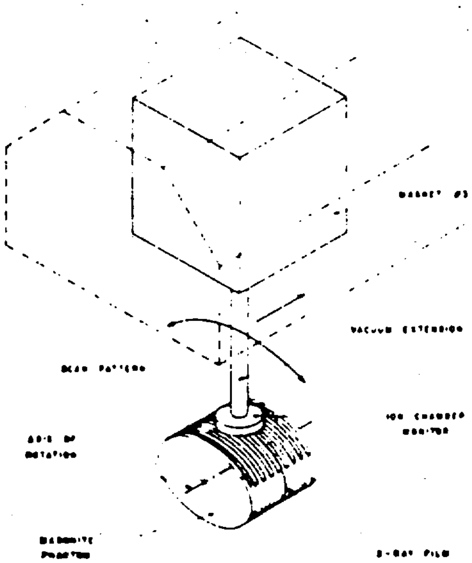

Fig. 5. Schematic drawing of experimental arrangement for irradiation of phantom in field scan.

radiation. In no case was a wet reaction observed and in rare instances did a severe dry epidermitis develop except when such reactions were deliberately produced by the addition of scattering material used in order to bring the biologic dose of radiation up to the skin surface. In the parotid tumors and oropharyngeal lesions, the sharp cut-off of mucositis reported by others was most striking. Dry mouths with thick ropy saliva have not been noted in these patients and we have altered our usual procedure of complete dental extractions in such patients and now remove only those teeth which will be included in the zone of irradiation.

One of the first patients treated had a mixed tumor of the parotid gland. She had noted swelling and a hard mass of the right parotid gland for 6 months. We used a special lucite template, such as we make for all specially shaped portals, and delivered a tumor dose of 6,000 rads at 5 cm. depth (Fig. 8). Twenty-eight treatments were given between July 6, 1959 and August 17, 1959. The energy of the electron beam was 14 mev. for the first 10 treatments and 11.5 mev. for the subsequent ones. At the

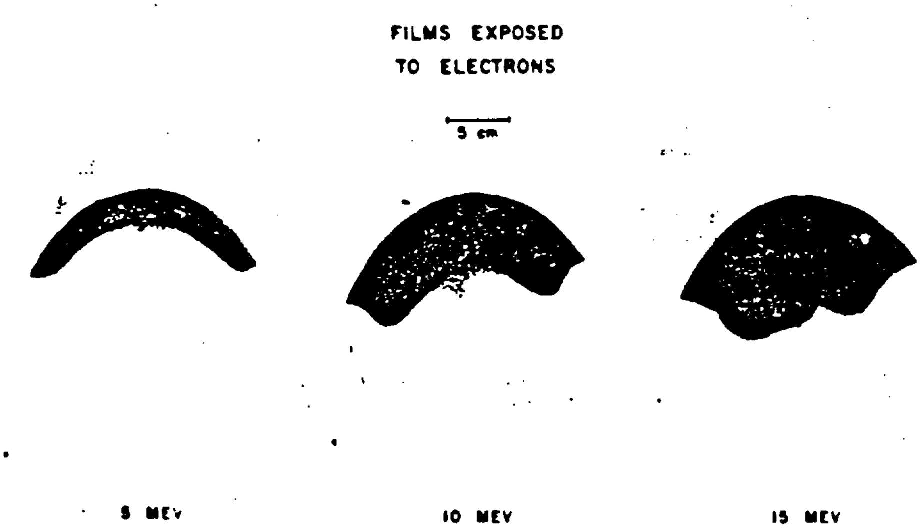

Fig. 6. Films exposed to arc scan beams of 5, 10 and 15 mev.

conclusion of therapy, the area of the single portal showed a moderate erythema which cleared rapidly. After 3 years there has been no evidence of recurrence and the skin appears normal except for a slightly coarsened texture (Fig. 9A).

The second patient to be described was first seen at our hospital in April of 1961, complaining of a growth on the upper gum. Several biopsies showed only leukoplakia, which was cauterized. The lesion grew in size however, and another biopsy showed squamous cell carcinoma. When we saw her, there was a large fungating lesion involving the left upper gingiva extending into the gingivobuccal gutter and having a plaque-like extension halfway across the palate. Using a single, 4.5×8 cm., portal and an electron beam at 20 mev., we planned a tumor dose of 6,000 rads. Treatment started on December 6, 1961. After 20 treatments and a tumor dose of 4,000 rads, the skin showed a mild erythema. The erythema was brisk with some bronzing at the time of the 31st treatment, at the tissue dose of 6,800 rads (Fig. 9B). Thirty-two treatments were given with a tumor dose of 6,300 rads, completing the course on January 17, 1962. The maximum tissue dose was 7,050 rads. Within 2½ weeks the skin reaction had almost entirely disappeared (Fig. 9C) and in 6 months the skin appeared normal (Fig. 9D).

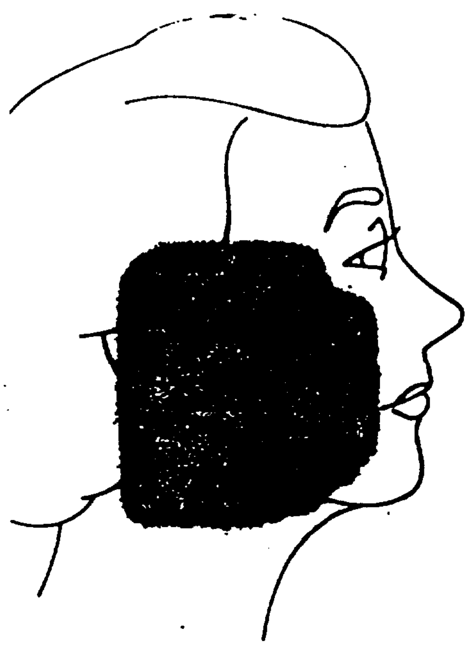

FIG. 8. Scan pattern used for electron beam therapy on a particular patient.

Another patient had a history of sore throat of 3 months' duration when seen in January of 1962. A fungating lesion involving the right vallecula, arytenoid, false cord and lateral pharyngeal wall was found. Biopsy showed squamous cell carcinoma in all areas. There was a large, very firm lymph node palpable in the right carotid triangle. The patient had a history of two myocardial infarctions in the past. A tumor dose of 6,400 rads was given in 36 treatments between January 15, 1962 and February 27, 1962. The maximum tissue dose was 7,900 rads. The electron beam energy was 20 mev. except for the last 9 treatments, which were given at 18 mev. The tumor dose was calculated at 8 cm., which was the 80 per cent level. One week before completion of treatment, there was a brisk erythema in the single 12×15 cm. portal. At 2 weeks after treatment, the erythema was subsiding and in 6 months

FIG. 7. Patient treatment area showing the final scanning magnet together with the vacuum chamber and transmission ionization chamber at the beam exit.

the skin appeared normal. The mucositis which appeared at 2,400 rads was severe at the end of therapy. The lymph node decreased in size but still remained as a 1 cm. hard nodule which has not changed in the last 8 months. There is edema of the right arytenoid but no evidence of tumor.

A patient with carcinoma of the tonsil was somewhat unusual. She had received 7,000 rads to the right tonsil for a squamous cell carcinoma in 33 treatments from September 28, 1959 to November 12, 1959. The radiation was given through a 180° sector of rotation, using the Co^{60} unit. In February of 1962 the patient was again referred for treatment, having developed a squamous cell carcinoma of the left tonsil. Because of the former irradiation, it was decided to use an electron beam in order to avoid the previously treated tissue as much as possible. An 8×11 cm. portal was used at 13 mev. for the first 17 treatments and an 8×13 cm. portal at 15 mev. for the last 7 treatments. A tumor dose of 6,450 rads was delivered between February 24, 1962 and March 31, 1962. The skin reaction at the completion of treatment consisted of a dry, scaling epidermitis (Fig. 9*E*) which subsided within a month (Fig. 9*F*). A maximum tissue dose of 6,800 r was delivered.

Quite a different problem was posed by a patient who was first seen in July of 1961, complaining of a mass in the nose and upper lip of 6 months' duration (Fig. 9*G*). She had a long history of soreness inside her nose and had been given 3 roentgen ray treatments 2 years previously and 4 more 1 year before. A biopsy showed squamous cell carcinoma. In this case we used 25 mev. electrons. In order to bring the maximum dose up to the surface of the lesion, a unit density wax mold was constructed. The patient received 35 treatments from August 2, 1961 to September 12, 1961 and the surface dose was 6,700 rads, with 5,560 rads at 9 cm. depth from the mold surface. A wet reaction resulted (Fig. 9*H*) but 9 months later the skin appeared almost normal (Fig. 9*I*).

DISCUSSION

There appears to be considerable disagreement between various authors as to the degree of skin reaction associated with electron beam treatment through single portals when the skin dose is in the neighborhood of 6,000 to 8,000 rads. Lochman[11] encountered wet skin reactions when the dose exceeded 7,500 rads. Zatz and his co-workers[21] have reported skin reactions comparable to those from orthovoltage roentgen therapy. There is also some disagreement as to the relative biologic effectiveness (RBE) of electrons. Lochman[11] concludes that the RBE is no greater than with roentgen rays and probably less.

The observations described in this paper suggest that the skin reactions are less than those reported by most of the authors quoted. There are a number of possible explanations which can be considered. Since the scanning beam traverses the area in a pattern similar to a television raster, it may be that there is an effect similar to treatment through a grid. However, the scanning is performed in such a way as to give a practically homogeneous surface dose, particularly when day to day variations in port positioning are considered. Another possibility is that with the pencil beam the radiation may be relatively clean as compared with a foil-scattered beam. Finally, the actual dose rate to the skin must be taken into account. This dose rate is 200 to 500×10⁶ rads per second. It may be that the latter part of the dose delivered to any cell is given during a period of relative anoxia, the bulk of the oxygen having been consumed during the first part of the time in which the dose is given. Dewey and Boag[4] found modification of the oxygen effect when bacteria are treated with large pulses of radiation as compared to unpulsed doses of the same amount given over relatively long periods of time.

SUMMARY

1. A partial review of the literature dealing with the clinical aspects of electron beam therapy is presented.

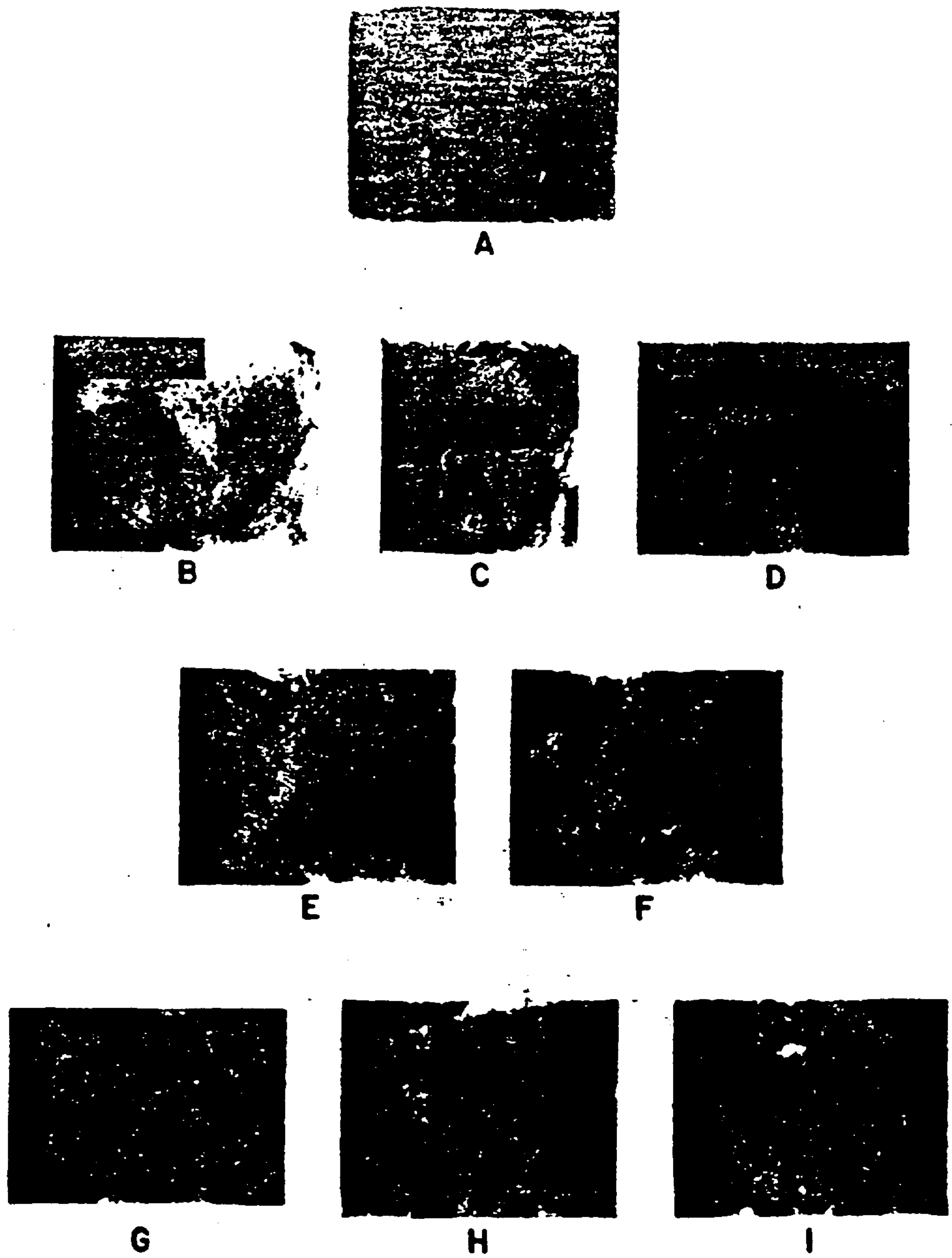

FIG. 9. (A) Appearance of skin of face in patient (H.C.) receiving a tumor dose (5 cm. depth) of [illegible] rads [illegible] years previously. (B) Skin reaction in patient (V.S.) at maximum tissue dose of 6,800 rads in [illegible] treatments. (C) Same patient (V.S.) after 2½ weeks. (D) Same patient (V.S.) after 6 months. (E) Skin reaction in tonsil portal in patient (N.M.). Tumor dose of 6,450 rads in 24 treatments. (F) Patient (N.M.) after 1 month. (G) Patient (A.McF.) prior to treatment. (H) Patient (A.McF.); wet reaction after [illegible] rads at surface of [illegible] in [illegible] treatments. (I) Patient (A.McF.) [illegible] months after treatment.

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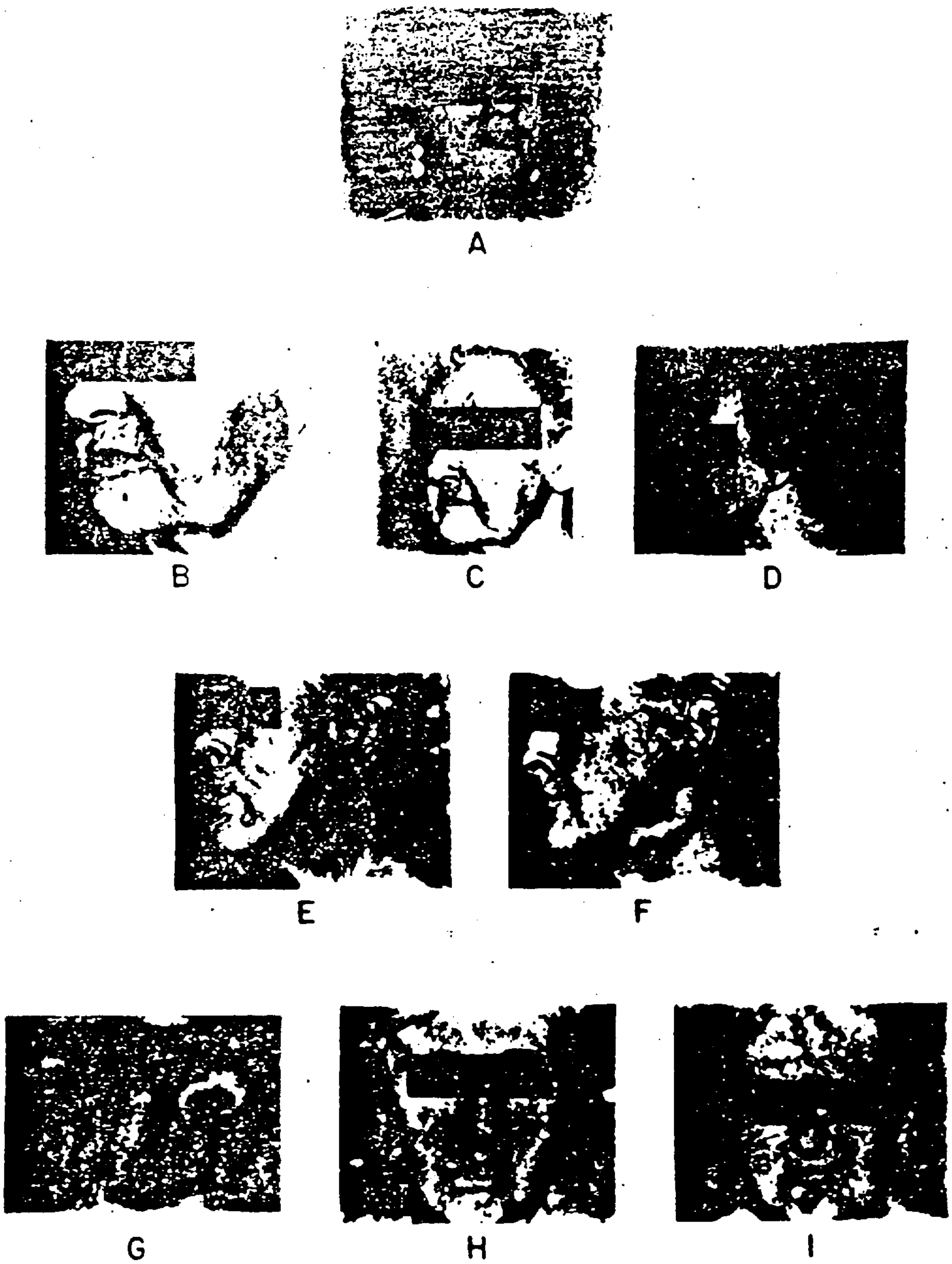
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2. A brief description of the pencil beam scanning electron linear accelerator at the Argonne Cancer Research Hospital is given.

3. Brief mention of the 97 patients treated by means of this device in the past 3 years is made.

4. The limited skin reactions observed are described.

5. Several theoretic explanations for the limited skin reactions are briefly discussed.

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