than the psoriatic type is good, more especially to A.C.T.H. therapy. In most patients the affection is cured or controlled, though individual requirements vary widely and maintenance therapy may need to be continued over long periods. With exfoliative dermatitis following psoriasis there was a ready tendency to relapse in those patients who showed an initial response, and one patient relapsed under treatment.

Eczema.—The response of eczematous reactions of the constitutional or exogenous type or from sensitization tended to be dramatic. In the latter group this response sometimes effected a cure, but relapse was usual following withdrawal of treatment in the other types of eczema. The response to treatment was less satisfactory in cases of seborrhoeic dermatitis and of nummular and varicose eczema. Hormonal therapy would appear to be useful in combating acute exacerbations of eczema and in facilitating the introduction and effectiveness of other lines of treatment. It may be that local therapy will prove valuable in this group.

Besnier's Prurigo.—The position here is the same as in the previous group so far as the acute eczematous aspects of the eruptions are concerned, but the effect of treatment upon chronic lichenification is usually less.

The results reported in all these conditions have to be considered in relation to the total dosage of the hormones administered; had larger doses or more prolonged treatment been used the response of the dermatoses might have been better, but the panel does not consider that the trial of larger doses is justified, in view of the risks involved.

A range of other dermatoses, including psoriasis, infantile eczema, urticaria, scleroderma, and pemphigus, has been investigated, and will form the subject of a subsequent report.

Summary and Conclusions

The results are presented of treatment of exfoliative dermatitis, eczema, and Besnier's prurigo by corticotrophin (A.C.T.H.) and cortisone.

In exfoliative dermatitis other than that following psoriasis the disease is controlled and often cured.

In eczema, except in the seborrhoeic type, there is a dramatic response, but usually a relapse following suspension of treatment except where an exogenic cause has been recognized and removed.

In Besnier's prurigo relief of symptoms is equally dramatic while the patient is under treatment, but there is less effect on the underlying lichenification.

A.C.T.H. and cortisone prevented or reduced the reaction to patch tests which had previously been positive.

Toxic reactions were encountered and are detailed. A few were of a serious character, but occurred in patients who were to be regarded as susceptible to such happenings.

The work of the panel was undertaken with A.C.T.H. and cortisone supplied through the Medical Research Council. Part of the cortisone came from a gift jointly to the Council and the Nuffield Foundation from Merck & Co. Inc., to whom the panel wishes to express its appreciation.

REFERENCES

- Downing, J. G. (1952). *New Engl. J. Med.*, **246**, 56.
Hopkins, J. G., Kesten, B. M., Nelson, C. T., Hambrick, G. W., jun., Jennings, R. G., jun., Machacek, G. F. (1952). *Arch. Derm. Syph. (Chicago)*, **65**, 401.
Jekel, L. G. (1952). *Ibid.*, **66**, 290.
Steinberg, C. L., and Roodenburg, A. I. (1951). *J. Amer. med. Ass.*, **146**, 1225.
Steiner, K., and Frank, L. (1952). *Arch. Derm. Syph. (Chicago)*, **65**, 524.
Sulzberger, M. B., and Baer, R. L. (1952). *Year Book of Dermatology and Syphilology*, p. 7.
— Sauer, G. C., Herrmann, F., Baer, R. L., and Milberg, I. L. (1951). *J. invest. Derm.*, **16**, 323.
West, B. M. (1952). *Arch. Derm. Syph. (Chicago)*, **65**, 56.

THE INHIBITION OF ACUTE X-RAY DAMAGE BY CORTISONE

BY

L. E. HOUGHTON, M.D.

Consulting Physician, Harefield Hospital, Middlesex

J. B. WALTER, M.D., M.R.C.P.

Institute for Clinical Research, Middlesex Hospital

AND

D. E. A. JONES, B.Sc., F.Inst.P.

Principal Physicist, Mount Vernon Hospital, Middlesex

An x-ray dose of 6,000 r delivered to an area of the skin of a guinea-pig will regularly produce inflammatory changes followed within sixty days by deep ulceration. The ulcers heal slowly and the irradiated tissues become shrunken and cicatrized. Evidence is presented to show that, if cortisone acetate is administered parenterally immediately before and after such irradiation, serious damage to the skin does not occur, within a similar period of observation.

Attempts have been made in the past to modify radiation damage to normal tissue; much work has been done in searching for agents capable of protecting animals from a lethal total-body exposure to ionizing radiations. Cysteine (Patt *et al.*, 1949, 1950) and D.C.A. (Ellinger, 1947) have been shown to exert some protection. The important role of the adrenals has been established, for when these organs are shielded during the exposure, mortality to radiation is decreased (Edelmann, 1951a), whilst adrenalectomized animals are more vulnerable (Edelmann, 1951b). Reports of the action of cortisone and corticotrophin on modifying the effect of total-body irradiation are contradictory. Smith *et al.* (1950) reported that cortisone does not protect mice, and this was supported by the experiments of Ellinger (1952). Wentworth and Billows (1952) suggested that there is even a synergic action between x rays and cortisone, while Thiersch (1952) found that this hormone inhibited regeneration of bone marrow following irradiation. On the other hand, Taber (1951) found that if the dose of x rays was not excessive corticotrophin provided a measure of protection against total-body irradiation in mice. Mirand *et al.* (1952) found that both D.C.A. and cortisone gave complete protection to mice following 500 r total-body irradiation, a dose causing 100% mortality in the controls.

Marshall (1953) found that the administration of cortisone to mice irradiated on the skin (3,000 r) produced a prolongation of the latent period before the onset of the lesions and apparent modification of their severity. There was, however, a good deal of overlap between the two groups, and the animals were watched for only thirty days after irradiation. The latent period was prolonged from 15.31 to 21.41 days (average) and no ulcers were produced in the 24 cortisone-treated animals, while this did occur in 7 of the 26 control animals. The cortisone was administered for short periods only.

In man, cortisone and corticotrophin have been used to modify the effects of radiation pneumonitis (Cosgriff and Kligerman, 1951) and also for radiation sickness (Taber, 1951; Houghton and Walter, 1953). The latter

also reported a case in which dysphagia occurring during x-ray treatment for carcinoma of the bronchus was controlled by corticotrophin.

Method

Thirty-eight young adult albino male guinea-pigs of the Dunkin Hartley strain were kept for one month on a standard diet and in separate cages. Their weights ranged from 390 to 690 g., 32 of the animals being between 500 and 650 g. They were divided into two equal groups, each animal being paired with one of similar weight. The average weight of the cortisone group was 568 g., while that of the controls was 572 g.

The backs of the animals were clipped and a suitable circular field (2.6 cm. in diameter) was marked. Special care was taken to avoid scars and scratches, and all fields were below the level of the adrenals. Immediately before treatment the animals were anaesthetized with 5 mg. of pentobarbitone sodium intraperitoneally. Each animal received a total dose of 6,000 r to the marked area in two equal doses, the second of which was delivered forty-eight hours after the first: the cortisone group and the controls were irradiated alternately.

Technique of Irradiation.—The x-ray beam was generated at 50 kV (constant potential) and 2 mA, using a Philips contact therapy apparatus. The x-ray tube, which had an end window, was fitted with a special brass applicator. This terminated in a short thin-walled "perspex" tube, the distal end of which, closed with a thin disk of perspex, was 2.6 cm. in diameter and 3 cm. from the focus. An internal circular lead diaphragm ensured that this perspex face, when in contact with the skin, exactly defined the irradiated area. The skin dosage rate, measured with full-backscatter on the surface of "mix D" tissue-equivalent wax (Jones and Raine, 1949) was 275 r per minute, so that the exposure time for each 3,000 r skin dose was 10 minutes 54 seconds. The x-ray beam had a 2.5-mm. aluminium filter, the half-value layer being 1.7 mm. Al. The short F.S.D. (3 cm.) ensured a rapid decline of dose rate in the subcutaneous tissues. It is estimated that the dose fell, at a depth of 1 cm., to a little less than half that received by the skin.

Cortisone Administration.—Twenty-four hours before the first exposure 19 of the animals received 10 mg. of cortisone acetate by subcutaneous injection into the anterior abdominal wall. This was repeated each morning throughout the period of observation. The cortisone group showed no marked toxic effects, and all the animals were given occasional feeds of dried peas and apricots to guard against potassium deficiency. The animals were inspected daily, and the onset and development of skin changes were recorded. For convenience, two grades of ulceration were recognized: (1) A superficial erosion where the lesion involved partial skin loss only. (2) A deep ulcer where the whole thickness of the skin was destroyed and the ulcer bed was composed of subcutaneous tissues. Such ulcers showed marked surrounding induration and were adherent to deep structures, features not shown by the superficial lesions. Deep ulcers were further subdivided into large and small, those over 4 mm. in diameter being placed in the former category.

Results

Seventy-one days after the irradiation 19 control animals (100%) showed large deep ulcers. The 19 cortisone-treated animals (100%) showed no ulcers. One of the latter showed a superficial erosion which healed within ten days.

Erythema and Epilation.—Erythema began on the 12th day and was present in 4 cortisone animals and 10 controls. During the next week epilation started, and by the 32nd day all the control animals showed complete loss of hair on the irradiated areas, by which time 16 had also ulcerated. The skins of all 19 controls showed marked erythema during the period of epilation. In the case of the cortisone group the erythema was less pronounced and the hair tended to remain adherent, being shed only when the skin desquamated.

By the 32nd day 16 still showed incomplete epilation and 2 showed practically no hair loss. Not until the 42nd day had all the irradiated areas epilated.

Ulceration.—All control animals developed deep ulcers, and the evolution of these is shown in the Chart. It can be seen that by the 59th day all had developed deep ulcers, and by the 71st day these were large. In contrast, only two animals of the cortisone group developed small deep ulcers, and these healed rapidly. Of the remaining 17 animals, 9 showed small superficial erosions which healed rapidly, while the remaining 8 showed no lesions at any time.

Contraction.—The size of the affected areas during the initial stages was identical in all animals. From the 32nd

Chart showing the development of ulceration in control and cortisone-treated groups: 19 animals in each group. ○=Superficial erosion. ●=Small deep ulcer. ■=Large deep ulcer.

day onwards contraction was noticed in the controls, and by the 71st day was present in all this group, being severe in six. This contraction was associated with ulceration, and became marked as the deep ulcers cicatrized and healed. No such contraction occurred in any of the cortisone group. By the 81st day six controls had healed completely with cicatrization, but ulceration persisted in the other control animals. Measurement of the fields showed pronounced contraction in all this group. Where the affected areas were no longer circular, maximum and minimum diameters were measured and the mean was found. On the 81st day the average mean diameter of the irradiated areas was 2.83 cm. for the cortisone group and 1.84 cm. for the controls. The minimum and maximum actual dimensions measured among the control group were 0.8 and 2.4 cm. respectively, the corresponding range for the cortisone group being from 2.5 to 3 cm.

Discussion

The results indicate that the administration of cortisone profoundly alters the response of skin to x-radiation. The epilation is delayed and the early erythema is lessened. The most striking effect is the complete absence of deep persistent ulceration, and it is noteworthy that the two deep ulcers which did appear in the cortisone group did not exceed 4 mm. in diameter and healed rapidly with little scarring. During

previous pilot experiments it was found that the effect of a given dose of x rays was by no means uniform or predictable even in a uniform group of animals. Ulceration sometimes occurred early or occasionally was delayed; an ulcer which had healed sometimes broke down again. Late effects of irradiation on the skin are being studied in this and other groups of animals, both with and without cortisone. It seems probable that the changes which we have observed in previous experiments, occurring after as long as eighteen months, are part of a different phenomenon. A dose of 6,000 r was chosen as likely to produce early deep ulceration in 100% of control animals.

Cortisone is known to inhibit inflammatory reaction of tissues to irritants of all kinds, and the suppression of this initial inflammatory reaction to radiation may prevent subsequent ulceration. It has been suggested by Järvinen (1951), however, that the suppression of the initial inflammatory response to ultra-violet light by cortisone is in fact a spurious protection, resulting in the end in increased tissue damage. A drug which occasionally produces severe irritation and presumably inflammation of the gastric and intestinal mucosa (P.A.S.) can be administered for long periods under the suppressive action of corticotrophin without resulting in damage to the mucosa (Houghton, 1954). If the protective action of cortisone to x-ray damage is in fact due to inhibition of inflammation, the hormone should be effective if given only during the time that these changes are taking place. The work of Marshall has indicated that this may be true in mice, in which he found that cortisone was most effective if started shortly before the appearance of the lesions. It is possible, however, that cortisone produces a protective action during the actual exposure to radiation. The hormone is claimed to inhibit mitoses in epidermal cells (Green and Ghadially, 1951), but it seems unlikely that this effect could produce the degree of protection that has been demonstrated in this experiment. Whether the protective action of cortisone is a direct effect upon the cells or whether the effects are through some indirect action is not known. Cholesterol is known to undergo chemical change when exposed to ionizing radiation, and it is possible that this is also true of cortisone. Experiments are proceeding, using hydrocortisone ointment locally, to ascertain whether the protective action is a purely local one.

The use of systemic cortisone in radiotherapy is limited by our lack of knowledge of whether or not the protective action is extended to malignant tissues. If it can be shown that tumour cells are not protected, then the administration of cortisone will have a twofold advantage: the undesirable and sometimes severe general effects of radiation are reduced if not altogether abolished; and, secondly, it would be possible to administer larger x-ray doses or to increase the volume of tissue irradiated without fear of excessive damage to normal tissues. On the other hand, the dangers of uncontrolled infection during cortisone therapy cannot be overlooked.

Quite apart from any clinical applications, the demonstration of the protective action of cortisone is of importance in that it shows one method of blocking x-ray damage. Since the fundamental mechanism of the destructive action of x rays is not clearly understood, a study of the protective action of cortisone may well lead to a better understanding of the biological effects of radiation.

It is believed that tissue damage resulting from exposure to nuclear-fission products does not differ essentially from that produced by x-radiation. It is possible, therefore, that the protective action of cortisone might be extended to this field.

Summary

A dose of 6,000 r was delivered to a circular area of skin in 38 guinea-pigs. The 19 control animals showed severe persistent ulceration and cicatrization, whilst the 19 animals receiving parenteral cortisone showed complete absence of such ulceration. Under cortisone the early erythema was reduced and the epilation delayed;

the irradiated areas showed no shrinkage, although this was marked in the control animals. The possible mechanism of the protective action of cortisone is discussed.

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REFERENCES

- Cosgriff, S. W., and Kligerman, M. M. (1951). *Radiology*, **57**, 536.
Edelmann, A. (1951a). *Amer. J. Physiol.*, **165**, 57.
— (1951b). *Ibid.*, **167**, 345.
Ellinger, F. (1947). *Proc. Soc. exp. Biol., N.Y.*, **64**, 31.
— (1952). *Ibid.*, **80**, 214.
Green, H. N., and Ghadially, F. N. (1951). *British Medical Journal*, **1**, 496.
Houghton, L. E. (1954). *Lancet*, **1**, 595.
— and Walter, J. B. (1953). *Lancet*, **1**, 798.
Järvinen, K. A. J. (1951). *British Medical Journal*, **2**, 1377.
Jones, D. E. A., and Raine, H. C. (1949). *Brit. J. Radiol.*, n.s. **22**, 549.
Marshall, A. H. E. (1953). *Acta radiol., Stockh.*, **39**, 73.
Mirand, E. A., Reinhard, M. C., and Goltz, H. L. (1952). *Proc. Soc. exp. Biol., N.Y.*, **81**, 397.
Patt, H. M., Smith, D. E., Tyree, E. B., and Straube, R. L. (1950). *Ibid.*, **73**, 18.
— Tyree, E. B., Straube, R. L., and Smith, D. E. (1949). *Science*, **110**, 213.
Smith, W. W., Smith, F., and Thompson, E. C. (1950). *Proc. Soc. exp. Biol., N.Y.*, **73**, 529.
Taber, K. W. (1951). *Radiology*, **57**, 702.
Thiersch, J. B., Conroy, L., Stevens, A. R., and Finch, C. A. (1952). *J. Lab. clin. Med.*, **40**, 174.
Wentworth, J. H., and Billows, J. A. (1952). *Radiology*, **59**, 559.

HODGKIN'S DISEASE

BY

RALSTON PATERSON, C.B.E., F.R.C.S., F.F.R.

AND

EDITH PATERSON, M.B., F.R.C.P.Ed.

From the Christie Hospital and Holt Radium Institute,
Manchester

Hodgkin's disease, or lymphadenoma, is a fairly well defined clinical and pathological entity when it presents in its classical form. It is, however, only one of a group of less well defined diseases of the lympho-reticular system, although a very distinctive one. Many borderline cases occur in which a crisp diagnosis of lymphadenoma cannot be made with certainty. According to the Registrar-General the annual death rate in England and Wales from Hodgkin's disease is 17 per million population. This is about one-hundredth of the death rate from all types of cancer taken together, or approximately equal to that from cancer of the tongue. Looked at from the point of view of general practice, Hodgkin's disease is therefore a relatively rare disease but common enough to need being kept in mind, in particular when a patient presents with otherwise unexplained lymph-node enlargement. Males are more often affected than females in the ratio of about 2 to 1. The disease predominantly affects persons of middle adult life at the time of their greatest working capacity, as shown in Fig. 1. This graph also demonstrates that childhood and old age are not exempt; we have, however, not seen a case in a subject younger than 2 years.

Pathological Features

The aetiology of Hodgkin's disease is still unknown. It is thought by many to be a generalizing neoplasm. Histologically the appearances sometimes resemble the sarcomas