.

1012.

Experimental Surgery.

THE EFFECT OF ACTH AND CORTISONE ON SKIN AND CONNECTIVE TISSUE.

.

يرود بيغيرو الإصراب الار

CARL SCHILLER, M.D.

Archibald Fellow in Plastic Surgery.

Submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the Degree of Master of Science.

April, 1952.

.

McGill University.

M. Sc.

PREFACE

This work was started in October 1949 as an Archibald Fellow in Plastic Surgery, and after a year was continued during a 2 year period of training in that specialty at the Royal Victoria Hospital. Much of the clinical work was carried out during this latter period. The helpful collaboration of Dr. G. Gavin Miller and Dr. J.S.L. Browne and of the Staff of the University Clinic of the Royal Victoria Hospital is gratefully acknowledged.

This research was aided by a grant from the Southam Company of Montreal. ACTH and Cortisone were supplied by the National Research Council of Canada.

As this study has ramified through various specialties - as Plastic Surgery, Experimental Surgery, Endocrinology and Pathology, I have had to call on a number of advisers, co-workers and friends to whom I now give my sincerest thanks. To Dr. Hamilton Baxter I am particularly grateful, not only for his ideas and suggestions which were the basis of this investigation but also for his guidance, stimulation and enthusiasm. Dr.D.R. Webster initiated me into the approach to animal experimentation and helped me greatly in avoiding the

i.

usual pitfalls of the neophyte. Many thanks are due to Dr. L. Johnson for his valuable suggestions and clinical assistance in the endocrinological management of our patients.

Many pleasant hours were spent with Dr. John H. Whiteside and Dr. Sidney Kobernick in reviewing the pathological material. I am deeply indebted to Dr. John Drummond and Dr. Martin Entin for many valuable suggestions; and to Doctors William Douglas, Cornelius O'Conor, Richard E. Straith, Herbert Lipschutz, Robert G. Randall for their cooperation and assistance in this project.

Technical assistance was most ably rendered by Mr. Paul Roustan and Mr. Jim Byers in the animal experiments in the Donner Building. I wish to extend my thanks to Miss Yvette Latondres for the preparation of the microscopic slides, to Mr. Harold Coletta and Mr. Charles Hodge for their excellent photographs and to Miss Charlotte Hall for her masterful deciphering and transcription of my hieroglyphics.

In ending I must express thanks to my wife - whose patience, forbearance and understanding helped me to carry on this investigation.

ii.

CONTENTS

Introduction	1
The Local Effects of Cortisone on Normal Skin	7
Cortisone Rubs to Scalp	1 <i>4</i> -
Local Cortisone in Hypertrophic Scars	16
Local Cortisone in Dupuytren's Contracture	20
Conclusions on Local Effects of Cortisone	26
Systemic Effects of ACTH and Cortisone	26
On Wound Healing in Rabbits	27
On Normal Skin in Rabbits	33
On Healing in Man	37
On Autografts in Man	47
On Homografts in Man	58
On Dupuytren's Contracture	75

INTRODUCTION

With Hench's (1) announcement of the dramatic effect of cortisone on rheumatoid arthritis - attention was suddenly focused on this hormone and on ACTH, the pituitary corticotropic hormone. These substances are by no means newly discovered. In 1935 - Kendall (2) isolated Compound E from the cortex of the adrenal, and in 1938, established its formula as 17 hydroxy - 11 dehydro cortico sterone. In 1946 Sarett (3) established a partial synthesis of this substance as a 24 hour procedure starting with a bile acid - desoxycholic acid.

This was the substance first used by Hench. Later, he found that ACTH (4) could also produce remissions in this condition - by a mechanism involving production of adrenal corticoids.

C. Smith (5) in 1930 demonstrated the affect of the pituitary on the adrenal cortex, as shown by the shrinkage of the cortex on ablation of the pituitary. In 1942 - Li and Simpson (6) isolated ACTH as a crystalline pure substance, while Sayer's, White, et al (7) working independently isolated it one year later. It is interesting to note that ACTH is almost diametrically opposed in many of its effects to the growth hormone of the pituitary.

Endocrines have long been known to exert a profound influence on skin and its accessory structures, and on the underlying connective tissue as may well be seen in the effects on wound healing. Selye (8) has pointed out the effects of ablation of various endocrine glands on wound healing. The absence of the adrenais retards the regeneration of tissue from available protein as shown by the comparison of liver reformation in starving adrenalectomized with similar non-adrenalectomized rats. Regeneration and wound healing are markedly impeded by adrenalectomy and restored to normal by the cortocoids, but not by adrenaline. Ablation of the thyroid remarkably impedes wound healing, but this is not significantly accelerated by thyroxine. Pancreatectomy impairs wound healing; however, this is almost completely improved with insulin, although lecithin and Vitamin C also play a role in this mechanism. In Cushing's syndrome, there is a well recognized weakness of the supporting tissues.

Under hormonal influences, the skin mirrors almost instanteous changes - such as flushing or blanching with anger - or breaking out in a cold sweat with fear. Chronic changes too - such as the atrophy of skin with loss of elasticity, premature graying, and loss of hair are found in debilitating diseases. Intense (Trepst & Petrie) or chronic (Brozels) psychic influences can also cause skin changes (9,10)- such as graying or general loss of hair, or dryness of hair and

skin. Other changes induced by the endocrines on skin may be summarized as follows. Hypophysectomy or Adrenalectomy causes cutaneous atrophy and loss of elasticity of the skin of animals (11). Snow and Whitehead (12) showed the antagonism between the pituitary growth hormones and ACTH on the skin of rats; ACTH causing thinning - while the growth hormone reverses the atrophy in hypophysectomized rats.

Large doses of dexoxycorticosterone in rats produces a psoriatic like scaly skin (13) with loss of hair. Houssay (14) showed that systemic cortisone in excess renders rat skin thin and atrophic, while Baker and Whitaker (15) showed that local applications caused thinning of skin and hair loss.

The skin adnexae are also affected. Thyroidectomy retards hair growth in rabbits (16) and rats, while thyroxine accelerates hair growth in thyroidectomized rats (17,18) underfed (19) and adrenalectomized (20) animals. Hypophysectomy retards hair growth (21,22) but it may be brought back to normal by pituitary extract injections, or by the transplantation of the hypophysis in rabbits (23). Ablation of the adrenals in young rats causes a precocious growth of hair; (24) while cortisone has been shown to inhibit hair growth (25). In rats deficient in the filtrate factor, the graying of hair was reversed by adrenalectomy (26). In rats (27,28) guinea pigs (29) and dogs (30,31) estrogens inhibit hair growth,

З

but this can be neutralized by androgens (32). Pregnancy (33,34) and corpus luteum (35) hormone retard hair growth. Sexual variation is shown by the more rapid growth of hair in male rats. However, when gonadectomized (36) - both grow hair at equal rates. Houssay & Young (37) found that in young rats, gonadectomy had no influence, whereas when performed later castration greatly accelerated hair growth (38).

Pigmentation of skin has been shown experimentally to be under hormonal influence. Forbes (39) has caused pigmentation of the nipple, areola, and external genitalia in guinea pigs with estrogens. Stilbesterol applied unilaterally to the nipple of the rabbit increases its pigmentation.

The fat in experimental animals has also been shown to be affected. Despite forced feedings - Baker et al (40) showed a loss of the panniculus adiposus in the rat receiving ACTH. The sebaceous glands in young rats is decreased in size by pituitary ablation (Snow and Whitehead) (40), by local application of DCA (42) and by ACTH parenterally (43). Growth Hormone on the other hand reverses the atrophy of sebaceous glands in hypophysectomized rats.(44)

Clinically, pathological endocrine states often are reflected in skin changes. To cite a few - the fine warm, moist skin of the hyperthyroid in contract to the thick dry skin of myxedema, the changes in vaginal epithelium with follicular hormones, the deepening in pigmentation seen in pregnancy, Addison's disease and myxedema; the cutaneous striae,

acne, hirsutism and moon facies seen in Cushing's disease and with prolonged administration of ACTH.

With the quick succession of reports of the many fields in which ACTH and cortisone manifested such dramatic changes (45) there appeared the conception of the influence of Compound E and F in connective tissue and collagen diseases. Ragan's report (46) on the inhibition of granulation tissue and wound healing brought questions into many surgeons' minds as to the method of choice in dealing with patients requiring surgery who were or had undergone therapy with these hormones. In plastic surgery it raised the question as to whether it would be possible to do skin grafting while receiving treatment; whether keloids, hypertrophic scars, and the hypertrophic fibroplasia of Dupuytren's Contracture could be mitigated by this means; and whether the antigen antibody response which was theoretically the cause of the loss of homografts could be eliminated by these powerful hormones. This last was highly accentuated by Whitelow's (40) widely published case.

Experiments were then designed to study the effects of these drugs in animals and man. Where feasible and possible to be carried out without injury or inconvenience to the patients, studies were carried out in man. The field of plastic surgery lends itself particularly well to the scheme - since in the course of various plastic procedures - as in the removal of unsightly scars or the creation of pedicles which are later removed - certain studies can be carried out without

detriment to the patient.

This investigation is therefore outlined in the following manner.

- 1. The Local Effects of Cortisone
 - A. On normal skin.
 - a. Intradermal.
 - b. Topical application.
 - B. On hypertrophied scars.
 - C. On Dupuytren's Contracture.

11. Systemic Effects of Cortisone and ACTH

- A. On wound healing in rabbits.
- B. On normal skin of rabbits.
- C. On wound healing in man.
 - a. Clean incised wounds.
 - b. Healing donor sites.
 - c. Healing skin grafts.

1. Auto skin grafts.

- 2. Homo skin grafts.
- D. Dupuytren's Contracture.

The Local Effects of Cortisone.

Introduction

Although a tremendous literature is in the process of being built up on the systemic use of cortisone and ACTH, very little has been done with regard to its local effects, save for a few isolated instances. Baker et al (48,49) showed that local application of cortisone in the rat caused thinning of the skin and loss of hair. Spies and Stone (50) showed the efficacy of cortisone in the treatment of iritis and conjunctivitis and in certain skin disorders as allergic dermatitis and chronic psoriasis, while Leopold, I.H. et al (51) used it in various ocular inflammatory diseases. Woods (52) used it both topically and in the anterior chamber and subconjunctivally in ocular conditions and experiments. Jones (53) inhibited rabbit corneal vascularization by local treatment. Hollander (54) compared cortisone and hydrocortisone as local agents in rheumatic joints. Baker and Whitaker (55) demonstrated interference in wound healing by the local action of adrenocortical steroids, while Baker and Coster (56) demonstrated that intradermal injections of 0.1 cc cortisone in rats caused cessation of growth of hair, thinning of the epidermis and dermis and atrophy of sebaceous glands. Conway and Stark (57) injected ACTH mixed with hyaluronidose into keloids relieving pain and itching, but not altering the appearance of the keloid.

In this study - an attempt was made to see the changes induced in normal human skin given by injection or by inunction; and into abnormal skin which was the site of either hypertrophied scar or Dupuytren's Contracture.

Intracutaneous Injections in normal skin.

A. Methods.

In one patient single doses of 0.1 cc cortisone were injected intradermally, and left for periods of time varying from 1 day to 2 weeks. In this case a 1/4" strip of normal skin adjacent to an area to be excised for extensive scarring, was injected at various intervals of time, and the entire strip removed at the end of two weeks. Thus, each site represented a period of reaction varying from 1 day to 2 weeks. The exact durations were 1 hur, 1,2,3,4,5, 7,9, 12 and 14 days. All sites were sectioned and studied microscopically. A second patient had a partial similar experiment carried out.

B. <u>Results.</u>

Case 1. Biopsy of normal skin 1 hour following intradermal 0.1 cc cortisone: (Fig.1) There is an area of basophilic fluid in the mid-dermal position. This is finely fibrillated and has separated the surrounding dermal fibres which have undergone no apparent alteration



Fig. 1: Biopsy of normal skin 1 hr. after injection of O.1 cc cortisone intradermally. The fluid is shown here distending the tissues and forming a pool like space which takes a light basophilic stain. This shows up poorly in the photograph. On close inspection, the crystals of cortisone can be seen. Little inflammatory reaction is present. H.P.S. X 100.



Fig. 2: Biopsy of normal skin 1 day after injection of 0.1 cc cortisone intradermally. The fluid is more basophilic; there is a moderate infiltration of polys into this area and a light inflammatory reaction around it. The surrounding dermal collagen shows little change.

of form or staining qualities. Throughout this area are evenly distributed crystals of cortisone - seen as small oblong refractile bodies, occasionally square or diamond shaped. There is very slight inflammatory reaction into this area save for a light infiltration in patchy areas of the surrounding dermis. There is also a mild perivascular infiltration about the blood vessels in the dermis - both near and also at some distance from the pool of cortisone. No epithelial changes are noted.

Biopsy of normal skin 1 day following intradermal O.1 cc cortisone. (Fig.2) Three small areas of cortisone pools are seen similar to the one described above but staining somewhat more darkly. The same crystals are seen and the reaction shows a moderate polymorphonuclear infiltration into this area with similar perivascular infiltration. The epithelium shows no changes.

Biopsy of normal skin 2 days following injection of 0.1 cc cortisone. This slide shows areas of fluid similar to those seen at one day, but the pools now have a more granular appearance. Many of the polymorphonuclear cells have degenerated. There is still a fairly marked perivascular infiltration for a fair distance about the site of injection, but half the cells present are now mononuclear. There is little inflammatory reaction in the immediate vicinity of the fluid pools. The adjacent collagen, erector



Fig.3 : Biopsy of normal skin 9 days after injection of 0.1 cc cortisone. The area is now eosinophilic; there is very little reaction but occasional mononuclear cells in patchy areas. There is still no recognizable change in the adjacent derma.



Fig. 4: Left: Control - Biopsy of a nodule in the palm of the left hand. Whorls of actively growing fibrous tissue are shown. Some older denser fibrous tissue is seen in the upper right corner.

Fig. 5: Right: 2 injections of 25 mg. of cortisone locally at weekly intervals. Biopsy taken 4 days later. Pool of cortisone seen at lower left corner. Note (1) lack of reaction. (2) No change in fibrous tissue. piloe muscle and epithelial cells of hair follicles are of normal appearance. No epithelial change can be seen.

Biopsy of normal skin 3 days after injection of O.l cc cortisone: The areas of cortisone have become more eosinophilic with a granular part in which nuclear debris can be made out. There are now a few macrophages about the area. A slight to moderate perivascular infiltration of lymphocytes and macrophages are present in the superficial layers of the dermis.

Biopsy of normal skin 4 days after injection of O.l cc cortisone. This is very similar to the third day.

Biopsy of normal skin 5 days after injection of O.l cc cortisone: The cortisone pools are somewhat more granular and homogeneous in appearance. The cellular reaction has decreased leaving only a few macrophages adjacent to the pool and a slight perivascular infiltration in the immediate vicinity.

Biopsy of normal skin 7 days after injection of O.l cc cortisone: This is very similar to the five day section.

Biopsy of normal skin 9 days after injection of 0.1 cc cortisone: (Fig. 3) The areas of cortisone injection is now poorly visualized - but is still granular with a few bits of nuclear debris. The occasional macrophage is

still present about the edge in patchy areas. There is still a moderate perivascular round cell infiltration in the superficial portions of the dermis.

Biopsy of normal skin 12 days after injection of 0.1 cc cortisone: There is only a slight perivascular infiltration in the superficial dermis similar to the nine day specimen. In the midportion of the dermis is a collection of macrophages with a moderate amount of pink staining cytoplasm. This is in the position of the previous pools of fluid.

Biopsy of normal skin 14 days after injection of O.1 cc cortisone: The block was serially sectioned and the only lesion found is a collection of lymphocytes, plasma cells and an occasional macrophage. This area is quite well vascularized compared to the surrounding dermis. The relation of this to the previous lesions is difficult to determine.

In none of the foregoing sections was any significant change seen in the connective tissue or epithelium of the skin.

Case 2. A similar study was carried out for a period of 1,2,3 and 4 days and showed similar findings for corresponding periods of time.

C. Discussion:

From these findings, it appears that upon injection of a small quantity of cortisone intracutaneously into normal skin, there is formed first a pool of fluid containing crystals of cortisone. These appear to distend the tissues at

the site of injection and produce only a mild inflammatory reaction - characterized by some polymorphonuclear infiltration and a mild perivascular infiltration. By the end of two days the polymorphonuclear cells in the infiltrate are decreasing and approximately half the cells are mononuclears. By the third day, the pools of fluid which were basophilic now become more eosinophilic, there are a few macrophages near the areas of injection, with some perivascular infiltration still present. By five days, the crystals cannot be clearly outlined; and there are still seen occasional macrophage, and similar perivascular infiltration. The seventh and ninth days show similar findings with the exception that the pools are becoming increasingly more difficult to find - while by the twelfth and fourteenth days the areas cannot be definitely established but may be represented only by small collections of macrophages.

From this - one can only venture to say that the cortisone may either be only very slightly irritating or that the drug itself inhibits any marked inflammatory response.

Cortisone Rubs to Scalp.

A. <u>Introduction</u>:

In an effort to determine to ascertain the effect

of inunction of cortisone on normal skin, 0.1 cc of cortisone (25 mg/cc) was dropped on a small area of the scalp at the nape of the neck and gently rubbed into an area approximately one cm. in diameter for a period of five minutes, two times daily. A control area on the opposite side of the neck was treated in similar fashion with a solution of cholesterol in saline.

B. <u>Results:</u>

Case 1. - R.D. 2 year old child being treated for congenital anomalies. Rubs were applied twice daily for 13 days, and biopsies performed.

Pathological report - Sections of these areas are essentially the same in all respects. There is a thin layer of keratin on the surface of both biopsies. The epithelium is 5 - 6 cells in thickness and no difference in morphology can be made out. The subpapillary blood vessels and those in the papillae are slightly dilated in both. There is an occasional perivascular round cell infiltration, but no marked inflammatory infiltration in either. The dermal collagen is of similar and normal appearance.

Case 2. - A.T. - 34 year old white female having large pedicle graft for radiodermatitis. Small similar areas on left back treated with rubs of cortisone and control

respectively for 30 days.

These sections showed no pathological variation from normal nor from each other.

an a construction and write, and a construction of the two constructions are presented and the construction of the test of test of the test of test of

Case 3. - J.W. - 5 year old girl undergoing a pedicle graft of the scalp. Cortisone and control rubs were carried out as described on contra-lateral areas of the nape of the neck for 34 days.

Sections of these two biopsies again showed no abnormal changes and no differences between the two areas.

C. <u>Discussion</u>:

In 3 cases, the rubbing of 0.1 cc of cortisone into a small area of normal skin for 5 minutes two times daily for periods varying from 15 to 34 days showed no pathological differences from normal or from controls of cholesterol in saline.

Cortisone injected locally into hypertrophic scar.

A. <u>Introduction</u>:

The effect of local injections of cortisone into 5 hypertrophic scars in two patients was studied for periods of time varying from 1 to 4 weeks. At the end of this period the scar was excised and the injected area studied microscopically and compared with a non-injected area.

B. <u>Results:</u>

Case 1. - S.P. - 16 year old boy undergoing plastic procedures for congenital absence of thumbs and ears. Several healing wounds of the abdomen had hypertrophied and formed disfiguring scars. Into one area 0.2 cc cortisone was injected daily for one week, a second area received 0.2 cc daily for 2 weeks, and a third area received 0.3 cc daily for 4 weeks. Because almost the identically same spot was injected each time - scrupulous detail toward asepsis was maintained; the area being scrubbed with phisoderm for 2 minutes before injection, and being dressed with sterile bandage following injection.

Grossly, it was noted that the mechanics of injection were difficult at first, but after the first few injections, the solution was able to penetrate more freely. Outside of a slight reddening on occasion no other gross changes could be noted in the scars. At no time was there any evidence of any inflammatory reaction. The patient never complained of any excessive pain - except that which accompanies most injections.

Biopsy of scar treated for 7 days: The epithelium shows moderate acanthosis with blunt or rounded rete pegs. The dermis is thickened and the collagen fibres tend to be parallel to the surface, and the papillary layer is partially

obliterated by the parallel collagen fibres. In the middle of the dermis is found a number of irregular pools of cortisone - containing similar crystals to those described above. The inflammatory reaction is confined mostly to this area, and is composed mostly of polymorphonuclear cells and cellular debris. There is no vascular reaction around these areas and no evidence of beginning organization. There is a moderate perivascular infiltration composed mostly of round cells with some polymorphonuclears and eosinophiles. The collagen bundles of the scar show no striking changes in morphology or staining - except in the immediate vicinity of these pools of cortisone, probably as a result of its mechanical factors.

Biopsy of hypertrophic scar treated for 14 days. The epithelium is similar to above. Some sections show pools which resemble those above, others are beginning to show the findings described in the section below. There are no discernible changes in the collagen adjacent to the pools of cortisone.

Biopsy of hypertrophic scar treated for 4 weeks with 0.3 cc cortisone daily: The epithelium is similar to the above, and the collagen is typical of a hypertrophic scar. Throughout two thirds of the section are scattered

areas of the injected cortisone in apparently different stages varying with their age. Some have the same characteristics described in the previous sections. The majority, however, show a peripheral zone of granulation tissue in which are many macrophages filled with gray finely granulated material. In some areas, foreign body giant cells are numerous. In some of the smaller areas, the pools have disappe ared leaving only large foamy macrophages and granulation tissue. The inflammatory reaction is very patchy and chiefly mononuclear in type. The collagen immediately above the areas of granulation tissue show some slight imcrease in activity - but is otherwise similar to the collagen not mear the injected material. No evidence of dissolution of collagen is noted. The accessory structures are not particularly remarkable.

١

المرجاح فالمتعاطية المردية المواجع

Case 2. - A.S. - 21 year old white female with a long hypertrophied scar in the left elavicular region secondary to a pedicle graft from the area used for reconstruction of an ear. This patient was treated with bi-weekly injections of 1.0 cc of cortisone into the same area of scar for 5 weeks. Grossly, the same findings were found as in the previous case with relationship to increasing ease of injection, lack of continued pain or inflammatory response. There was no discernible change in the lesion. No pathological study is available since the patient refused operation until some time after the study was concluded.

C. <u>Discussion</u>:

Repeated daily injections of cortisone in the amounts and for the periods described failed to cause any definite clinical or microscopic changes in hypertrophic scars. It was noted that the latter injections were easier to make than the earlier ones, but this may well be a mechanical basis rather than a direct effect of the The microscopic analysis is difficult to evaluate hormone. since the reactions of the injections given at different times are superimposed on each other. The seven day treated scar shows areas of only mild inflammatory reaction near the pools of cortisone, with some perivascular infiltration of cells which apparently vary with the duration of cortisone at that site. There is this same similarity in this to the reaction seen in normal skin. The tissue which was treated for a longer period of time - 4 weeks - shows a peripheral zone of granulation tissue, macrophage with finely granulated material and in some places - giant cells - resembling in nature a foreign body reaction.

The Effect of Local Cortisone on Dupuytren's Contracture.

A. <u>Introduction</u>

In this condition there is a pathological involvement of the palmar fascia characterized histologically by two

phases. The active phase is represented by well vascularized proliferating fibroblastic tissue with numerous vesicular nuclei. At a later stage, there is found only dense cicatricial tissue which has squeezed out all the fat and deeper structures of the skin. (Bunnell).

In the hope of causing a regression of the lesion with cortisone, the following study was carried out.

Cortisone acetate was injected into hypertrophied palmar fascia in five patients. The duration of the condition varied from one to twenty years and the severity of the involvement from mild to severe. Two patients received only 2 injections at weekly intervals while the remaining three received 7 injections, usually twice a week. The first dose of cortisone was 12.5 mg. in a volume of half a c.c. Subsequently, injections were of 25 mg. in a volume of one c.c. The material was injected into the tendon-like contracted cords of hypertrophied palmar fascia or into discrete nodules when these were the major pathological feature. The hormone was not injected into one spot, but was spread through the nodule or contracted cord as much as was feasible. In the latter instance considerable pressure was required to force the solution into the firm scar-like tissue. Biopsies of the hypertrophied palmar fascia were taken; in two cases before and after treatment; and in one, after treatment only. Plaster models were made prior to injection in three cases, and also

following cessation of therapy.

and the second second

B. <u>Results</u>:

Case 1. - F.C. - 48 year old white male with 4 year history of Dupuytren's Contracture. The site of maximum involvement was the right ring finger. A small biopsy was taken, and 1 cc of cortisone given and repeated in one week. The palmar fascia was excised at operation 10 days later. No clinical improvement was noted.

الالتحالي المتعطيتين الا

Biopsy of the treated area shows the typical pools of cortisone in areas of older Dupuytren's tissue. There is a moderate perivascular inflammatory reaction. No definite changes in the collagenous and fibroblastic can be found in comparison with the control.

Case 2. - G.P. - 42 year old white male with 7 month history of contracture. One c.c. of cortisone was injected into the palmar scar on the 1st and 8th days and biopsy taken on the 11th day. No clinical improvement was noted.

Here again several pools of cortisone were found in the denser more compact less actively growing fibroblastic tissue. No effect was found on the collagen save for a mild inflammatory reaction with an infiltrate of lymphocytes, plasma cells and macrophages. (Figs 4 and 5)

Case 3. - E.S. - 70 year old white male, with long standing history of Dupuytren's Contracture and previous operation for this condition 3 years before.

He received weekly injections of 1 c.c. of cortisone into several nodules on his hands for a period of 2 months, and a biopsy was taken two weeks later. Clinically, there was no improvement.

Biopsy showed the usual slight reaction to the pools of injected material. There was no discernible morphological alteration of the dense fibrous tissue forming the Dupuytren's tissue.

Case 4. - D.H. - 44 year old white male with history of 10 year duration of Dupuytren's Contracture. He was operated on 2 years before and had a recurrence in the form of a grape sized nodule at the base of the 5th finger. He received 6 weekly injections and no subjective or clinical improvement was noted. No biopsy was taken.

Case 5. - C.S. - 50 year old white male with 9 year duration of disease. Maximum involvement was present in the left small finger. He received weekly injections of 1 c.c. cortisone into these three areas for 7 weeks, at the end of which time no subjective or clinical improvement was noted. No biopsy was taken.

C. <u>Discussion</u>:

Clinically no significant decrease in the size

23]

of the nodules or increase in ability to extend the fingers was noted in 5 patients. The patients observed no change and this was confirmed by careful observation and by comparison of plastic casts. There was no appreciable difference between comparable areas of the control biopsies and biopsies of the treated areas which showed crystals of cortisone in proximity to the dense fibrous tissue seen in Dupuytren's Contracture. No deposits were noted in immediate contact with areas of actively proliferating fibroblasts although these were often situated nearby.

CONCLUSIONS

1. The injection of 0.1 cc of cortisone intracutaneously in normal skin produces only a mild inflam atory reaction, characterized by very little reaction adjacent to the injected material and a moderate perivascular infiltration. The cells of the infiltrate are first polymorphonuclear, and change very quickly to mononuclear cells and macrophages. This may be due either to lack of irritation of the injected material, or inhibition of the inflammatory response by cortisone.

2. O.l cc of cortisone rubbed into a l cm. area of normal skin twice daily failed to produce any recognizable morphological changes either clinically or microscopically in the skin or its appendages in three cases when maintained for a period up to 34 days.

3. Repeated local injections of cortisone into hypertrophic scars failed to cause any clinical or morphological changes in the connective tissue.

4. Repeated injections of cortisone injected into 5 cases of Dupuytren's Contracture for a period up to 7 weeks failed to cause any clinical or microscopic regression of the lesion.

The Systemic Effect of Cortisone in Rabbits.

INTRODUCTION

Following a traumatic or operative wound, the stages of healing may be divided into two phases. First, that of inflammation or a lag period during which injured or necrotic cells are removed. The lag period usually lasts until about the third or fourth day; however, its length varies with the degree of tissue damage, infection and location of the wound. Second, that of wound repair which consists primarily of cellular proliferation and secondarily of maturation of the scar. When the edges of a wound have been approximated there is an exudation of fibrin and leucocytes which fills the space between the cut surface and which acts as a framework through which fibroblasts and capillaries proliferate. The cellular proliferation comprises epithelium which divides, spreads and restores the surface continuity. The deeper tissues are repaired by fibroblasts; these branch and deposit collagen fibrils so that union of the wound becomes increasingly firm. This proliferation is evident from the fourth day onward.

These normal stages of wound repair may be affected by both systemic and local factors. Systemic factors such as age, general metabolic state, nutrition, haematologic abnormality, or concomitant systemic disease may markedly alter the

rate of healing. Similarly, local factors such as crushing of tissue, restriction of blood supply, inadequate apposition of wound edges, infection, the type and number of sutures used and movement of the part will affect the healing from the local standpoint.

It has been shown recently in the rabbit that ACTH or cortisone retard the growth of all elements of connective tissue (58) and the growth of granulating tissue in open wounds (59) as well as that about fractures (60). Plotz and associates (61) found that flooding rabbits with vitamin C did not block the hormone effect on granulation tissue. The same inhibitory effect on wound healing has also been shown to occur in the mouse (62).

It was decided to study the effect of cortisone on rabbits both in regard to its influence on wound healing and also the possibility of causing atrophic changes in the skin. The obvious clinical implication of this study might be the prevention of overgrowth of granulation and scar tissue in wounds in man, thus preventing hypertrophic or keloid scarring.

WOUND HEALING

A. Methods:

Healthy male albino rabbits of the same strain weighing between two and three kilos, were fed a standard diet of

Purina chow.

Following preliminary experiments with twelve rabbits to determine suitable dosage, a group of three were injected with three, six and nine mg. per kg. of cortisone daily, the middle dosage representing approximately the maximum dose administered to man in relation to respective body weights. The hair of the back was removed very close to the skin with a special electric clipper, and the skin was prepared with green soap, alcohol and zephiran. Four control wounds were made on the left side of the back extending from the upper thoracic to the lumbar region. Each incision was two cm. long and was carried completely through the skin and panniculus carnosus. The wounds were sutured with two No.35 stainless steel wire sutures which were permitted to remain throughout the course of healing. Dressings were not applied, and all wounds appeared to heal without evidence of infection. Biopsies were taken from the median segment of each of the four control wounds on the fourth, seventh, tenth, and fourteenth days postoperatively. The specimen was removed with the wire sutures in place to prevent separation of the wound edges caused by trauma of the biopsy removal. These were fixed in ten per cent formalin. After the control biopsies had been obtained the animals were injected for three days with cortisone to permit time for maximal absorption and physiologic action of the hormone to develop. Then,



Fig. 6 Control wound 7 days postoperatively. There is evidence of proliferation of fibroblasts and capillaries with union of epithelium and wound surfaces. Haematoxylin and eosin X 100.



Fig. 7 Treated wound in same rabbit as Fig. 6 after parenteral injection of 3 mg. of cortisone daily for 7 days. Note separation of both epithelium and wound surfaces with little evidence of fibroblastic or capillary proliferation. Haematoxylin and eosin X 100. wounds of the contralateral areas on the right side of the back were made in a similar fashion, and treatment of hormone continued for a total of fourteen days, biopsies being obtained on comparable days.

B. <u>Results:</u>

The rabbit receiving nine mg. of cortisone a day showed a loss of 29% of body weight, while the rabbit treated with six mg. maintained a constant weight. The remaining rabbit, injected with three mg. of cortisone, gained 17% over his initial body weight. Gross examination of the wounds of the rabbits did not reveal any observable difference between control and treated wounds.

The sections were stained with haematoxylin and eosin and Weigert's elastic tissue stain.

In Table 1 the healing of the individual wounds in the rabbits has been broken down into some of its components. It will be seen that fibroblastic proliferation, capillary proliferation, and physical union by epithelium and granulation tissue in the treated wounds, lagged behind the control wounds (Figs. 6 -9). Collagen formation closely paralleled the growth of fibroblasts, the first appeared in the seventh or tenth day biopsies. The treated wounds showed a greater tendency for haemorrhage to occur into the into the incision line. A rather striking observation was that while the epithelium in the treated biopsies showed a proliferative activity

	4 days		7 days		10 days		14 days		
	Control	Treated	Control	Treated	Control	Treated	Control	Treated.	
3 MG. Rabbit #38R									
Proliferation of fibroblasts. Proliferation of capillaries. Epithelial union Granulation tissue union	Slt. N.S. Abs. Abs.	Slt. Slt. Abs. Abs.	Slt. Slt. Pres. Abs.	Slt. Slt. Abs. Abs.	Abun. Abun. Pres. Pres.	Mod. Slt. Abs. Abs.	Abun. Abun. Pres. Pres.	Biopsy lost.	

TABLE 1

Effect of cortisone on wound healing.

6 MG. Rabbit #29

Proliferation of fibroblasts.	Mod.	Slt.	Abun.	Mod.	Abun.	Slt.	Abun.	Mod.
Proliferation of capillaries.	Mod.	N.S.	Abun.	N.S.	Abun.	N.S.	Abun.	Mod.
Epithelial union	Pres.	Abs.	Pres.	Abs.	Pres.	Pres.	Pres.	Pres.
Granulation tissue union	Abs.	Abs.	Pres.	Abs.	Pres.	Pres.	Pres.	Pres.

9 MG. Rabbit #38L

Proliferation of fibroblasts	Mod.	Slt.	Abun.	Mod.	Abun.	Mod.	Abun.	Mod.
Proliferation of capillaries	Slt.	Slt.	Mod.	N.S.	Mod.	Slt.	Abun.	Mod.
Epithelial union	Pres	Abs.	Pres.	Pres.	Pres.	Pres.	Pres.	Pres.
Granulation tissue union	Abs.	Abs.	Pres.	Abs.	Pres.	Pres.	Pres.	Pres.


Fig. 8 Control wound 7 days postoperatively. There is abundant proliferation of fibroblasts and capillaries with union of epithelium and granulation tissue. Haematoxylin and eosin X 100.



Fig. 9 Treated wound in same rabbit as above after injection of 6 mg. cortisone daily for 7 days. Both epithelial and granulation tissue union are absent although there is moderate fibroplasia. Haematoxylin and eosin X 100.

only slightly less than that of the control wounds, the former did not unite firmly until the tenth day in any of the rabbits as compared with epithelial union of the control wounds on the fourth and seventh days, respectively. In spite of the absence of, or only slight proliferation of capillaries in the treated animals, the fibroblasts were still able to effect union. However, the growth of the fibroblasts was neither as fast nor as abundant as in the control wounds. In both the control and treated wounds there was no evidence of infection. Only a few lymphocytes and an occasional polymorphonuclear leucocyte were present in any of the wound biopsies.

C. <u>Discussion:</u>

Although only three rabbits are included in this study, it is evident that in the range of dosage of cortisone administered parenterally quite definite inhibitory effects were observed on granulation tissue formation. Of the factors studied, the significant change was a quantitative decrease in proliferating fibroblasts and capillaries. This inhibition is reflected in a delay of filling in of the wound space and development of firm union of the wound edges. Our observations on epithelial proliferation agree with those of Ragan and associates (59) but firm union of the proliferating edges with each other was delayed until the loth postoperative

day in all treated wounds (Figs. 7 and 9). This lack of firm union may be due to a deficiency of the epithelium or to lack of support by granulation tissue.

Because of the known individual differences in response to cortisone, a large number of animals would be required to establish the effect of variation in dosage. Therefore no conclusions with reference to this point may be drawn from our material. However, these rabbits received doses of cortisone within the range administered to patients, in proportion to their respective body weights.

It appears evident that one of the many actions of cortisone is to inhibit inflammatory reaction and to reduce excessive fibroblastic proliferation. This hormone may cause changes in the connective tissue cells so that they no longer react to their usual stimuli. This effect may possibly be due to an alteration in cell permeability.

Systemic Effect of Cortisone on Normal Skin of Rabbits.

A. Methods:

Baker et al (63) have demonstrated that parenteral injection of ACTH in the rat causes thinning of the epidermis, and atrophic changes in the sebaceous glands and panniculus adiposus. Therefore - as an additional study in the experiment described above, the skin and its accessories were studied both in the control and the treated animals at the time that the study on wound healing was conducted.

B. <u>Results:</u>

Changes in the skin of the treated animals at a distance from the wound were noted in all rabbits (Figs. 10 and 11). These first appeared on the thirteenth day of treatment in the rabbits receiving three and six mg. and on the tenth day in the animal injected with nine mg. of cortisone. The first changes observed were a "crinkling" of the skin surface and a condensation of the collagen of the dermis. Later changes included a thinning of the epidermis with a loss of polarity of the basal layer, and a partial to complete disappearance of the basal cells. The dermal collagen condensed to a further degree, with a thinning or disappearance of the adipose layer between the dermis and muscularis carnosus. The hair follicles became smaller and their bases tend to recede toward the surface. These changes were all present in each rabbit by the seventeenth day of treatment, the day the last biopsy specimen was taken. No difference in the number or size of the capillaries could be determined. Mitotic figures were present at infrequent intervals in the epithelium of all specimens, and were found with approximately the same frequency in the treated and control biopsies.



Fig. 10 Normal appearance of rabbin skin showing normal epithelium, dermis and skin appendages. Haematoxylin and eosin X 40.



Fig. 11 Skin of same rabbit after treatment with 9 mg./ kg. of cortisone for 17 days. Note "crinkling" and thinning of epidermis, condensation of dermal collagen and partial atrophy of hair follicles. Haematoxylin and eosin X 40.

C. Discussion:

It was therefore possible to confirm in the rabbit treated with cortisone the findings of Baker and his co-workers in the rat. If these atrophic changes would be produced in man as a side effect of treatment with cortisone - it would be most undesirable. This question is studied later in this report.

Green (64) has reported that 1 mg. of ACTH suppressed mitosis in mice for several hours and from this observation made some general statements on the mode of action of this hormone on various body tissues. Only the epithelium in these cases was studied for mitotic figures. Their presence were noted in both treated and control animals, and occurred with equal frequency in both.

CONCLUSIONS

(1) Cortisone was found to have an inhibitory effect on the healing of incised wounds in the rabbit.

(2) This inhibitory effect resulted in a depression of growth of fibroblasts and capillaries. Firm union of the epithelium was delayed.

(3) Atrophic changes were caused in the epidermis, collagen fibres, hair follicles and panniculus adiposus of rabbits by the parenteral injection of three, six, and nine mg. per kg. of cortisone.

Systemic Effect of ACTH on Healing in Man.

Several investigators (65,66,67) have reported clinical observation of delay in healing of biopsy wounds in patients receiving parenteral therapy for various diseases, such as rheumatoid arthritis, lupus erythematosus, psoriasis, dermatomyositis and periarteritis nodosa. However, no control wounds were made. In a recent paper (68) the effect of adrenocorticotropic hormone on the healing of wounds in two patients has been described. The periods of observation were four and seven days respectively.

This investigation was undertaken because of several considerations. First, it is quite erroneous to assume that man must respond in an identical manner to the usual laboratory animals such as the rat or rabbit, on which much of the previous work with ACTH or cortisone on wound healing has been carried out, particularly when excessive doses in relation to their respective body weights are administered. It is most probable that their pituitary-adrenocortical response or some other mechanism may differ qualitatively or quantitatively. Second, due cognizance should be taken of the fact that the response of one individual with a systemic disease may vary considerably from that of a healthy person when both are treated with equal doses of the same hormone. Accordingly, it was decided to study not only the influence of ACTH on healing of incised wound but also -on skin grafts, and on dermatome donor areas where healing is

mainly effected by epithelial proliferation and to a relatively minor degree by granulation tissue. Controlled clinical and microscopic studies were carried out for as long as fifteen days on healing of incised wounds and dermatome donor areas, while the autografts were biopsied at intervals for twenty- . three days.

A. Methods:

CARGE SECTION AND

Five patients with various disease conditions such as rheumatoid arthritis, psoriasis, or atopic dermatitis, and one healthy male who had been admitted for a minor pedicle flap procedure were included in this group. These patients with one exception received at least 100 mg. daily of ACTH intramuscularly for varying periods of time, which were administered in divided doses. The patients were placed on a controlled dietary regime which was maintained throughout the course of their stay in hospital. Evidence of response to hormonal action as measured by drop in eosinophiles, as well as other clinical and laboratory data were noted in all cases. The healthy patient who was admitted for plastic surgery showed very definite evidence of adrenocortical stimulation. With one exception, all patients were permitted the freedom of the ward so that de-conditioning from prolonged bed rest would not occur. The healing of the control wound situated on either the abdomen or thigh was compared with that of a similar wound on a contralateral site which had been created at

the beginning of the period of hormone therapy.

The wounds, made under local anaesthesia, varied between 8 and 10 cm. long and were carried through the skin well into the subcutaneous fat. They were sutured at 0.5 cm intervals with 00000 dermalon sutures. A uniform type of dressing composed of xeroform gauze held firmly in place with gauze dressings, bandage and adhesive was applied to each wound. Biopsies were taken during the healing of both incised wounds. Donor areas and skin grafts were biopsied at various intervals from four days to as long as twentythree days. The sutures were removed between the third and seventh postoperative days, as indicated.

B. Results:

Case 1:

M.H. female, aged 36, was admitted for treatment of rheumatoid arthritis.

A wound was made on the left lower abdomen on the same day that ACTH therapy was started. She received 100 mg. of hormone intramuscularly in divided doses for seven days. Biopsies were taken on the fourth, seventh and eleventh postoperative days. On the day that hormone treatment ceased, a control wound was made on the contralateral side and this was biopsied on the fourth postoperative day. She showed a good urinary corticoid and clinical response.

Pathology. Treated wound: The fourth day biopsy (Fig.12) showed only slight epithelial proliferation , the wound edges were split apart and a considerable quantity of haemorrhage had occurred into the wound. Fibroblastic and capillary proliferation were not seen. The seventh day biopsy showed epithelial union and immediately beneath the epithelium a small zone of proliferating fibroblases were present. The neighbouring capillaries were dilated but proliferating capillaries were not found. Only an occasional active appearing fibroblast was seen throughout the remainder of the depth of the incision. In the eleventh day biopsy taken four days after cessation of therapy, the entire depth of the incision was united by proliferating fibroblasts. Numerous capillaries were now invading the incisional area. Collagen fibres could be made out in the upper one third of the wound.

Control wound: The fourth day biopsy (Fig.13) taken after cessation of therapy showed firm epithelial union but only minimal fibroblastic activity, and no evidence of capillary proliferation. It should be noted that the healing of this wound occurred in the fourth day post ACTH period when the patient might still have been in a hyperadrenocorticoid state.

Case 2:

S.G. male, aged 47, was admitted for treatment of generalized psoriasis and minimal arthritic symptoms. A control



Fig. 12 Case 1 : Biopsy of treated wound - 4 days postop. Pt. received 100 mg. ACTH daily. There is haemorrhage in the wound with slight epithelial proliferation, and very little fibroblastic and capillary proliferation.



Fig. 13 Case 1: Same pt. with wound created on day of cessation of therapy, and this biopsy taken 4 days postoperatively. Firm epithelial union, but little fibroplasia and no capillary proliferation. Question of persistent hyperadrenalism after biopsy arises. wound was created on the right thigh and biopsies were taken on the fourth and seventh postoperative days. Therapy with 100 mg. of ACTH daily was started on the 7th postoperative day and continued for 7 days. A second wound was made on the contralateral side on the day of commencement of ACTH therapy and this wound was biopsied on the fourth and seventh postoperative days. Under the same conditions, dermatome donor areas on the abdomen, 0.016 inch in depth, were observed for healing. Biopsies were not taken of the donor areas, but gross evidence of complete epithelization of each area was noted on the 8th postoperative day. The patient showed slowly developing urinary corticoid response, symptoms of arthritis were only partially relieved, and the psoriasis became worse.

Pathology. Control and treated wounds: The fourth day biopsies both before and with therapy were essentially similar and showed good epithelial union with a few active appearing fibroblasts scattered throughout the length of the incision. The wound edges were separated by fibrin clot. Both the control and treated biopsies revealed the same degree of healing on the seventh day, with the entire wound bridges by vascular granulation tissue and united by healthy epithelium. (Figs. 14, 15).

Case 3:

E.H. male, aged 54, was admitted for treatment of rheumatoid arthritis. A skin incision was made on the left thigh which



Fig. 14 Case 2: Biopsy of control wound 7 days postoperatively. Epithelial union is firm and there is vascular granulation tissue uniting the wound surfaces throughout their entire length. H. & E. X 60.



Fig. 15 Case 2 : Biopsy of treated wound 7 days postoperatively. Although the wound is wider and a tongue of fat has intruded, there is epithelial union and granulation tissue formation equivalent to that of the control. The epithelium situated to the right of the fat tongue is proliferating from a hair follicle. H. & E. X 60. was biopsied on the third, sixth, tenth, thirteenth, and seventeenth postoperative days. ACTH was started on the third postoperative day and discontinued on the tenth. On the first day of therapy, 200 mg. of ACTH was administered; on the second, 150 mg.; on the third 100 mg., and so continued in decreasing doses until the seventh day when 25 mg. was given. His urinary corticoid response was poor but the rheumatic signs and symptoms were improved by therapy.

Pathology. The third day biopsy was united by epithelium and a fibrin clot. A slight proliferation of fibroblasts and capillaries was evident in the wound edges.

The sixth day biopsy showed epithelial union but the wound edges beneath the epithelium had separated to allow a fat tongue to herniate up to the epithelium. Slight fibroblastic activity was noticed at the edges of the wound beneath the epithelium and scattered active appearing fibroblasts were seen along the wound edges. Capillary proliferation was not evident as in the prior biopsy.

The tenth day biopsy showed vascular granulation tissue bridging the incision in the upper portion and in the succeeding biopsies there was progressive flattening of the epithelium and fibrosis of the depth of the incision and of the intruding fat tongue.

Case 4:

J.A. female, aged 27, was admitted for treatment of psoriatic eczema. This was markedly improved while receiving hormone

therapy. This patient received 60 mg. of ACTH for nine days. On the day that this course of therapy was discontinued, an incision was made on the right thigh and this wound was biopsied five days postoperatively. A second wound was then made on the left thigh five days after cessation of the first course of treatment. From the following day, 60 mg. of ACTH daily was given until the fifth postoperative day when the second wound was also biopsied.

Pathology. Control wound: (Fig.16) The fifth day biopsy after therapy was discontinued showed firm epithelial union with numerous proliferating fibroblasts and capillaries beneath the epithelium, along the wound edges, and invading the fibrin clot.

Treated wound: (Fig. 17) The fifth day biopsy after therapy was reinstituted showed immature epithelial union and a much less extensive fibroplasia. Capillary proliferation was not evident.

Case 5:

V.S., male, aged 35, was admitted for a pedicle flap operation. A control wound was made in the right lower abdomen approximately ten cm. long, and it was biopsied on the fourth, seventh, tenth and fifteenth postoperative days. At the same time, a 0.016 inch thick skin graft was removed from the right upper abdomen. The donor area was dressed in routine manner



Fig. 16. Case 4 : Biopsy of control wound 5 days postoperatively. The epithelial union is firm and granulation tissue may be seen invading the edges of the fibrin clot. H. & E. X 60.



Fig.17 Case 4 : Biopsy of treated wound 5 days postoperatively. The epithelial union is less mature and proliferating fibroblasts can only be seen at the edges of the epithelium. There is no fibroblastic activity in the depth of the wound. H. & E. X 60. with Bettman's gauze and gauze dressings. This donor area was biopsied on the seventh and fifteenth postoperative days. Both control and treated donor areas first appeared healed to gross inspection on the ninth day.

Fifteen days after the control wound and donor area were made, the patient was started on intramuscular injections of 100 mg. of ACTH daily in divided doses for thirteen days, when it was gradually tapered off to prevent acute withdrawal symptoms. On the first day of therapy with ACTH a contralateral wound ten cm. long was made on the left abdomen. An autograft 0.016 inch thick was applied to a freshly denuded area where a tube pedicle flap had been raised. Biopsies of these areas were made at time intervals comparable to the various control wounds and grafts. This patient showed a marked response to hormone therapy as indicated by a drop in eosinophiles, increased weight with "moon" facies, euphoria, moderate increase in blood pressure and transient glycosuria. After cessation of therapy his symptoms subsided promptly.

Pathology. The fourth day wound biopsies with and without therapy showed no essential difference. Both showed epithelial union with only slight fibroblastic and capillary proliferation in the dermis. In the two seventh day biopsies, the proliferative activity of the granulation tissue was equal but was quantitatively less in the treated wound. The control wound showed partial dermal union whereas the treated wound did



Fig. 18 Case 5: Biopsy of control wound 7 days postoperatively. The epithelial union is firm. Granulation tissue is present throughout the wound with union in the upper portion. The disruption of the epithelium and upper portion of the dermis on either side of the wound is an artefact. H. & E. X 45.



Fig. 19 Case 5: Biopsy of treated wound 7 days postoperatively. The epithelial union is firm and granulation tissue is present in the upper portion and along the right side of the wound, but without union. H. & E. X 50.



Fig. 20 Case 5: Biopsy of treated wound 10 days postoperatively. Excellent epithelial and granulation tissue union is present throughout the wound with the formation of collagen fibres. The vertical tears are due to artefacts. H. & E. X 50.



Fig. 21 Case 5: Biopsy of treated donor area 7 days postoperatively. The regenerating epithelium can be seen spreading over the surface from a hair follicle. Slight fibroblastic activity is present only about the upper part of the hair follicle. H. & E. X 60. not (Figs. 18,19). In the tenth day wounds the treated incision (Fig.20) showed good granulation tissue union throughout its length. The control incision could not be compared due to the inclusion of foreign material (keratin) in the biopsy area. Both the fifteen day wounds showed firm fibrous union with numerous collagen fibres.

The seven day healing of the treated donor area showed good epithelial regeneration from hair follicles and sweat ducts with little fibroblastic activity (Fig. 21). The seven day control was spoiled in the preparation of the section. The fifteen day healing of the donor areas was well advanced in both biopsies but the epithelium of the control was thinner and more compact, and the granulation tissue layer was wider and better formed as compared with the treated area (Figs. 22, 23).

Biopsy of the autograft by the seventh day showed a good granulation tissue union with its bed. The graft had retained a normal healthy appearance and the capillaries were dilated (Fig. 24). There was little inflammatory cell infiltration of any type. Clinically the gross appearance of this large autograft throughout the healing period up to thirty days postoperatively showed no deviation from the ordinary course of healing.

Examination of all specimens revealed no evidence of atrophic changes of epithelium, dermis or skin appendages which



Fig. 22. Case 5: Biopsy of control donor area 15 days postoperatively. This shows good healing of a normal donor site. H. & E. X 60.



Fig. 23. Case 5: Biopsy of treated donor area 15 days postoperatively. The epithelium is less mature and the underlying granulation tissue layer is thin and irregular with few capillaries. H. & E. X 60.

could be attributed to hormone therapy.

C. Discussion:

A study of wound healing is beset by many difficulties. Man is the most desirable subject for such a project since species difference in response need not be considered and complete cooperation may be obtained in avoiding exposure of the healing area to trauma, infection or other variable factors. It is known that there is variation in the rate of healing not only in different individuals but also in the same individual in health, and disease. Contralateral wounds in the same person, studied in sequence, help to reduce to a minumum the systemic factors such as age, general metabolic state, nutrition, haematologic or systemic disease.

Certain phases of hormonal behaviour should be reviewed. The effective dose of ACTH varies widely among different individuals. As Thorn (69) has observed it may cause varying adrenal steroid output because of differences in functional activity of the adrenal gland in different people. In determining the dosage required in a given case, the level of esoinophiles, urinary steroids and other laboratory data provide merely a general index that the patient has responded. But the quantity of hormone required to cause alteration in pathological processes, wound healing, etc., may be quite different from that requited to produce the above mentioned indices. Moreover, when



Fig. 24. Case 5: Biopsy of autograft 7 days postoperatively. The graft has a healthy appearance. Active granulation tissue may be seen uniting the graft to its bed. The haemorrhage seen at lower left corner is due to trauma. H. and E. X 60. the adrenal "fires" following an operation, the quantitative response depends upon the amount of hormone produced, and its effect depends not only upon the responsiveness of the pituitaryadrenal system but also upon the general status of the individual and his tissues at the time. It may be considered that in the use of this hormone, initial dosage should be sufficient to evoke definite evidence of adrenocortical stimulation. Body weight, blood pressure, eosinophiles, occasional urinary and blood sugar determinations should be performed. A rapid gain in weight and appearance of oedema may necessitate a lower salt diet, diuretics or a lowering or cessation of hormone therapy. A rise of blood pressure chould also be watched for as well as the development of a diabetic state. Psychological changes such as euphoria or hypomania may develop. Another difficulty is the obscuring of many of the symptoms and signs of disease under ACTH or cortisone treatment. For example, peritonitis can occur without fever. The patient may not be "toxic", abdominal rigidity may be absent, and the white blood count already raised by ACTH may rise no higher (70).

Output of endogenous ACTH by the pituitary gland is decreased when this hormone is administered, o the dosage should be reduced gradually over a period of several days to permit reestablishment of output of endogenous ACTH. Selye (71) has shown that mineralo-corticoids such as DOCA caused increased oedema and

inflammatory reaction in local formalin induced arthritis whereas ACTH or cortisone prevented this effect. It is believed that ACTH stimulates principally the liberation of glucocorticoids (resembling cortisone) from the adrenal. There is, of course, a possibility of failure or response of the adrenal to ACTH in some individuals.

Some of our patients experienced more marked improvement in symptoms and signs of the disease from which they suffered than others. Laboratory studies which were carried out simultaneously in four cases (72) revealed considerable variation in response. With one exception these cases received 100 mg. of ACTH daily in four doses at six hour intervals for varying periods of time.

Wound Healing:

Comparison, under control conditions and under therapy with ACTH, of wounds of skin and subcutaneous tissues showed a variable and apparently unpredictable response in different individuals. The fact that some patients showed delay in wound healing and others did not may be referable **ei**ther to a variation in adrenal response, or in reaction of the tissues to the same amount of adrenal hormone.

Dermatome donor areas - Contralateral donor areas were studied in two patients. In the first patient (Case 2) both treated and control donor areas were clinically healed on the

eight postoperative day. In the second patient (Case 5) both donor areas appeared healed grossly on the ninth postoperative day. Microscopic examination of biopsies of the latter showed somewhat more mature healing in the control than in the treated area.

Skin grafts - Interesting observations were made on the one normal patient who received also an auto-skin graft. The autograft which was applied when hormone therapy was begun showed no delay in union with its bed, either grossly or on microscopic examination, which observation was well correlated with the healing of his incised wound and donor area.

Atrophic changes in the epidermis, collagen fibres, hair follicles and panniculus adiposus due to parenteral therapy with cortisone have been reported in the rat (73) and have been seen in the rabbit as described in the previous chapter. We failed to note any of these changes in man receiving ACTH for as long as two weeks. However, striae have been observed in both Cushing's syndrome and patients treated for prolonged periods with ACTH and cortisone.

CONCLUSIONS

1. The effect of doses of the order of 100 mg. of ACTH daily for periods up to 2 weeks on wound healing, epithelization of donor areas, autograft and homograft survival, and on

skin was studied.

2. The rate of healing of incised wounds of skin in man may or may not be delayed by ACTH under these circum-stances.

3. In those cases in which a delay of healing occurred, the pattern of healing of the wounds was unaltered.

4. This variation in rate of wound healing may be due either to a variation in adrenal response, or in reaction of the tissues to the same amount of adrenal hormone.

5. The normal rate of healing of an autograft was not delayed.

6. Epithelization of donor areas was not retarded.

7. Atrophic changes of skin or its appendages were not found.

8. Parenteral administration of ACTH is sometimes accompanied by serious side effects which demand careful clinical and laboratory supervision of each case.

The Effect of ACTH on the Survival of Homografts in Man.

Introduction

Many investigators have endeavoured to find some method of obtaining permanent survival of skin homografts. The vision of a skin bank where compatible grafts could be stored in quantity, as we now use blood, bone, cartilage and cornea, has stimulated a great deal of experimental work. The possible future use of stored homoskin grafts, so grouped or treated that permanent survival might be as confidently anticipated as that of autografts, would be a development of major importance in the treatment of extensive loss of skin from burns or trauma. The possibility of mass civilian and military casualties requiring skin grafting should stimulate research into new procedures in skin homografting as actively as search for new antibiotics were accelerated by World War 11.

The reports (74 - 84 incl.) of successful homografting of skin between other than identical twins have not been convincing because in many instances the patients were not observed for sufficiently long periods of time, or a sequence of biopsies was not taken. The rapidity with which marginal epithelium from the host will extend and resurface or grow beneath a residual plaque of denuded homograft dermis has not been fully appreciated and has result in misinterpretation; also, surviving hair

follicles or sweat glands buried in granulation tissue frequently proliferate so extensively that the homograft may be replaced in a short period by a sheet of regenerated host epithelium growing beneath the homograft which appears to provide a protective cover. With regard to transplantation of skin from one monozygotic or identical twin to another (85,86,87,88,89) it has been pointed out (90) that this procedure is "autografting" not "homografting", a term which has been used and which may have caused some confusion.

The bulk of both clinical and experimental observation confirms without question that homografting is not a procedure which permits permanent survival of the foreign graft at all, or at least in any practical percentage of cases. Three theories have been formulated to explain this incompatibility: (1) The blood group therapy. (2) The cellular theory. (3) The active immunity theory. The latter is currently the theory most widely accepted. The skin homograft is thought to form antigens which evoke the production of antibodies by the host and the graft is eventually destroyed by the subsequent antigen-antibody response. During the degenerative stages and sloughing of the skin homografts, the number of plasma cells and lymphocytes and sometimes eosinophiles which are deposited in the graft steadily increase. Since these cells are thought to be concerned with the production of antibodies, some positive evidence is provided for this theory. Further,

it has been shown in the rabbit (91) that repeated application of homografts results in more rapid degeneration and loss of the second set grafts. This has been confirmed and extended in man (92) when as many as five sets of homografts have been applied from the same donor to the same recipient on fresh raw areas.

Because of the known inhibition of tissue reaction to antigens and changes in antibody formation evoked by parenteral injections of ACTH and cortisone it was decided to study the effect of parenterally administered ACTH started at various time intervals following the application of skin homografts in man.

Methods and Results.

Case 1:

V.3., aged 36, blood group B. Rh+ (Fig.25). Healthy male undergoing pedicle flap procedure. When a tube pedicle was constructed, a homograft of skin 0.016 inch thich from an unrelated donor whose blood group was A.Rh+ was applied to a fresh raw bed. Fifteen days later, before this graft had lost its epithelium or showed gross signs of sloughing a second homograft 0.016 inch thick and nine square inches in area was applied from another unrelated donor whose blood group was A. Rh+. At the same time an autograft thirty-two square inches in



Fig. 25 Case 1 : This pt. had a homograft (H-1) applied on the lst day, which sloughed in routine fashion, at the onset of ACTH therapy (16th day) a second homograft (H-11) and autograft were applied. The clinical gain of weight, increase of blood pressure and euphoria is shown, with laboratory evidence in form of eosinopenia. The time relationship of the biopsies are also shown.



Fig. 26 Case 1: Biopsy of treated homograft - 7 days postoperatively. The graft has taken well and only slight degenerative changes are seen.

area was applied to an adjacent raw bed. Parenteral therapy with 100 mg. of ACTH was given daily in four divided doses and continued for fifteen days. This was discontinued because of hyperadrenocorticoidism. During the period of hormone therapy, the first homograft lost its epithelium and degenerative changes terminating in sloughing occurred before treatment with ACTH ceased. In view of the fact that the first homograft took and lived for fifteen days before the treatment period started, the course of the second homograft and autograft, which were applied just before hormone therapy was instituted, provided further data.

والمحصور ويشهرون

The autogenous and homogenous skin grafts took completely without delay and the latter was quite normal in appearance up to nineteen days. A biopsy of the autograft taken on the seventh day of ACTH therapy showed a good granulation tissue union with its bed. The graft had retained a normal healthy appearance and the capillaries were dilated. There was little inflammatory cell infiltration of any type. The gross appearance of this large autograft throughout the healing period, as long as 3 months postoperatively, showed no deviation from the ordinary course of healing of such grafts. Biopsies of the autograft were taken on the seventh and thirtieth postoperative days. Examination of all specimens revealed no evidence of atrophic changes of epithelium, dermis or skin appendages which could be attributed to hormone therapy.

The second homograft, applied at the commencement of ACTH therapy and biopsied at seven days (Fig.26), showed slight epithelial degenerative change and slight proliferation of the Only a few dilated capillaries were seen throughout rete pegs. the graft. There was a slight perivascular and diffuse inflammatory cell infiltration, chiefly polymorphonuclear leucocytes and a few eosinophiles. Many of the capillaries contained red blood cells showing the graft was still vascularized. The granulation tissue formed at the junction was irregular and meagre in amount. Biopsied on the fifteenth day (Fig.27), the epithelium showed slight acanthosis and spongiosis with somewhat more prominent degenerative cellular changes. In the dermis the degenerative changes in the collagen were slightly more marked than in the seventh day section with some pyknosis of nuclei. The capillaries were infrequent in the graft but contained red blood cells. There was an irregular fibroblastic ingrowth from the graft bed. The inflammatory infiltration was increased from the seventh day biopsy, and now consisted largely of lymphocytes and eosinophiles. Grossly the homograft appeared as healthy as the autograft until the nineteenth day when the epithelium began to desquamate, and on the twenty-second day had been completely lost over one half of the graft.

A biopsy taken on the twenty-third day (Fig. 28) showed marked degenerative changes throughout the homograft with almost complete loss of epithelium. The surface was covered by a necrotic and purulent exudate. An extensive infiltration of polymorphonuclear and eosinophiles was present.



Fig. 27 Case 1: Biopsy of treated homograft 15 days postoperatively. Slightly more advanced degenerative changes in epithelium and collagen are present. The inflammatory infiltration is increased in amount and is chiefly mononuclear in type. H. & E. X 60.



Fig. 28 Case 1: Biopsy of treated homograft 23 days postoperatively. Marked degenerative changes are now present with only a very small amount of degenerating epithelium remaining (see arrow). A heavy acute inflammatory cell infiltration is present. H. & E. X 60. The capillary walls were necrotic and small haemorrhages had occurred. Therefore, it is considered that in this case the survival of a homograft applied at the onset of therapy was not prolonged by 100 mg. of ACTH therapy daily for 15 days.

Case 2:

G.M., aged 24, blood group O Rh+. This patient was admitted to hospital suffering from flame burns of his back and right arm; and in addition to the usual burn therapy he received ACTH in equally divided doses commencing one day after the accident and continuing for thirty-two days. After six days of ACTH therapy, a homograft of skin, 0.016 inch thick and 6 square inches in area from an unrelated donor (blood group O Rh+), was applied to a raw bed where a large pigmented nevus had been removed. Biopsy of the homograft after 15 days, showed that the epithelial cells of the graft were oedematous with early degenerative changes. The collagen fibres of the dermis were similarly affected and had lost their normal fibrillary character. The graft was firmly united to the bed by a broad zone of proliferating fibrous tissue. A considerable inflammatory infiltration was present throughout the dermis and extended into the epithelium and a number of polymorphonuclear leucocytes were present. Some of the capillaries contained blood cells. Biopsy of the graft on the twenty-third postoperative day revealed that it was now represented only be remnants of

collagen fibres which were covered by necrotic tissue and fibrin. The graft was being invaded by actively proliferating oedematous granulating tissue and was heavily infiltrated by acute inflammatory cells. The original junction of graft with the underlying bed was now occupied by well formed fibrous tissue.

Case 3:

L.M., aged 45, blood group 0 Rh+, was admitted for treatment of burn contractures of the left arm. Following release of the contracture of the arm and application of a large autograft 0.016 inch thick to the antecubital fossa, a homograft of the same thickness from an unrelated donor whose blood group was A Rh+ was sutured into a raw bed created on the upper part of the arm by excision of scar tissue. Parenteral therapy was 100 mg. of ACTH administered in equal divided doses twice daily in Adactor solution which prolongs the period of absorption of hormone, was started immediately following the operation. After thirteen days the amount of hormone was gradually reduced until it was discontinued on the thirty-second day. Both autogenous and homogenous grafts took completely and appeared quite normal. The appearance of these grafts is shown on the fifteenth postoperative day (Figs. 29 and 30). Biopsies of both grafts showed considerable variation in appearance on histological section. The autograft was firmly united to its


Those on the left (Figs. 29,31,33) show the progressive disintegration of the homograft applied at the same time and biopsied at similar periods. The graft which has taken well on the 15th day (top) is wrinkled on the 23rd and desquamated completely by the 28th day.

bed by granulation tissue and only slight oedema of epithelium and dermis was present. On the other hand, there was moderate inflammation of the epithelium and dermis of the homograft characterized by oedema and inflammatory cell infil-The inflammatory cells were mononuclear with a few tration. eosinophiles. The small blood vessels of the graft contained red and white blood cells. Only slight granulation tissue formation was present at the junction of the graft and its bed. The epithelium of the homograft began to separate on the twentieth day, and Figs. 31 and 32 show the difference in appearance between the auto and homografts on the twenty-third postoperative day. The marked variation in histological appearance was revealed on microscopic examination. At this time the autograft was well united to its bed with collagenous tissue. There was little evidence of oedema. The epithelium was assuming its normal appearance and the dermal collagen was normal in character. A slight lymphocytic infiltration was present in the interstitial tissue. Geveral hair follicles were seen in the graft and the epithelium of these was normal, although the hair shafts were degenerative. Biopsy of the homograft on the twentythird day revealed rather marked degenerative and inflammatory changes in the dermis. The epithelium which had been separated from the dermis in numerous areas by an accumulation of fluid, was lost during preparation of the section. The dermal papillae were still visible in the section. The inflammatory reaction

was now entirely mononuclear in type. Proliferating capillaries were seen in the graft dermis, although there was little granulation tissue formation at the junction of the graft and its bed. The completely normal appearance of the autograft (Fig.33) may be contrasted with total loss of the homograft (Fig.34) with the exception of a few fragments of dermis on the twenty-eighth postoperative day. On microscopic examination the homograft was now represented only by a narrow zone of necrotic tissue in which a few remnants of collagenous fibres could still be recognized. This tissue was being invased by proliferating capillaries and fibroblasts from the graft bed. A considerable inflammatory cell infiltration was present and this included numerous polymorphonuclear leucocytes.

Case 4:

A CONTRACTOR OF A CONT

In a previous patient - V.S. described on page (45), a study on homografts was also carried out. On the commencement of his therapy with ACTH, an autograft and homograft, each 0.016 inch thick were applied to a freshly denuded area when the tube pedicle graft had been raised. The patient had received a homograft from a different donor two weeks previously. The blood groups of the patients were incompatible. Biopsies revealed the following. The treated homograft, biopsied at seven days, showed little epithelial degenerative change and

only slight proliferation of the rete pegs. Only a few dilated capillaries were seen throughout the graft. There was a slight perivascular and diffuse inflammatory cell infiltration, chiefly polymorphonuclear leucocytes and a few eosinophiles. Many of the capillaries contained red blood cells. The granulation tissue formed at the junction was irregular and meagre in amount.

In the fifteen day treated biopsy of the homograft, the epithelium showed slight acanthosis and spongiosis with somewhat more prominent degenerative cellular changes. In the dermis the degenerative changes in the collagen were slightly more marked than in the seven day section with some pyknosis of nuclei. The capillaries were infrequent in the graft but contained red blood cells. There was an irregular fibroblastic ingrowth from the graft bed. The inflammatory infiltration was increased from the seventh day treated biopsy and now consisted largely of lymphocytes and plasma cells with a few polymorphonuclear leucocytes and eosinophiles. Clinically the homograft appeared as healthy as the autograft until the ninteenth day when the epithelium began to desquamate and on the twenty-second day had been completely lost over one-half of the graft. A biopsy taken the next day showed marked degenerative changes throughout the homograft with almost complete loss of epithelium. The surface was covered by a necrotic and purulent exudate. An extensive infiltration of

polymorphonuclear leucocytes and eosinophiles was present. The capillary walls were necrotic and small haemorrhages had occurred.

The uneventful healing of the autograft has already been described in this case (Page 50).

Case 5:

H.S., aged 48, blood group A.Rh-, was admitted for reconstructive covering of a partially amputated foot by "cross leg" pedicle flap. During the course of this procedure the patient had an autograft 0.016" in thickness applied to the donor site of the pedicle flap; and also a homograft taken from an unrelated donor 3 hours before. The donor's type was A.Rh+. The patient received 200 mg. of cortisone orally from one week before up to and during the entire course of observation of the graft (for an arthritic condition of the hands which had recurred). In this case, the graft was cut very thin; and when checked on the micrometer scale of the microscope, it was found to measure 4-5 thousandths of an inch in thickness. (Fig. 35)

In this excellent review on homografting Rogers (90) suggested that thin homografts might be less antigenic than thicker ones; and that epithelium alone might be the solution to the problem. While this graft was in a proportion of equal parts of epithelium and derma, its ultimate



Fig. 35 Case 5: Section of thin homograft 4-5 thousandths of an inch contrasted to a graft approximately 20 thousandths of an inch thick. Note that proportion of dermis to epidermis of the thin graft approximates 1:1.



Case 5: Thin Homograft. Patient receiving 200 mg. oral cortisone daily from 1 week before application through period of observation. Fig. 36, Left: 12 days postoperatively. The graft has taken but is showing signs of degeneration.

Fig. 37, Right: 24 days postoperatively. The graft is lost. Only a small amount of dermis remains.

fate was the same as that of the thicker grafts. Actually, this graft sloughed in less time than the others as illustrated in (Figs.36,37).

.

Discussion and Conclusions.

While only four patients with application of five homografts of skin under ACTH therapy, and one with cortisone, have been studied, they provide useful information because of extensive and correlated laboratory, pathologic and clinical records. ACTH therapy was delayed until fifteen days after the application of one homograft, started on the same day as skin grafting in two grafts and in one patient with extensive burns treatment with ACTH was carried out for six days before the homograft was sutured into the fresh recipient bed. In this way the timing of the effect of ACTH on the homografts was varied, so that possible differences in reaction during the sequence of stages of healing of a graft could be observed.

In only one instance were the major blood groups and Rh factor of the skin graft donors and recipients compatible and in this instance the homograft sloughed off in the customary fashion.

An observation which has been noted by many investigators, but which should be emphasized, is the rapidity with which a homograft will slough and granulating area will be resurfaced with epithelial ingrowth from the margins. Comparison of figures 31 and 33 in which there was a time interval of five days will stress this point.

To achieve uniformity in reporting results (92) the length of survival of the epithelium of the homograft was taken as the end-point, since collagenous remnants of the dermis frequently persist in some cases for long periods before final disintegration.

The "active immunity" theory, which attempts to explain the incompatibility and eventual loss of skin homografts due to an antigen-antibody response appears to receive no support from our results with ACTH which is known to block the symptomatic manifestations or certain allergic and anaphylactic reactions.

Furthermore, Rogers hypothesis that their homografts might be more permanent than thicker ones was not found to hold in one case where the proportion of dermis to epidermis was 1 to 1, and while the patient was receiving cortisone pre - and postoperatively.

Further work is necessary with ACTH and other hormones before final conclusions may be drawn. Perhaps new hypotheses should be formulated to explain the failure of permanent take of homografts, so that experimental work from a quite different approach may be undertaken in an effort to solve this most difficult problem, which has possibilities of wide clinical application.

Cortisone in Dupuytren's Contracture

Systemic Cortisone, Preoperatively.

A. Introduction:

Clinically Bunnell (93) has admirably described the disease as follows "Apparently the condition is associated with a diathesis which leads to overgrowth and thickening and contracture of ligamentous tissue. Part or all of the palmar fascia and its vertical components undergo various degrees of thickening and contracture". Furthermore - he has been impressed by the fact that people with this condition show a marked limitation of the joint motion on slight provocation.

Since this condition is primarily one affecting connective tissue - and particularly fibroblasts, it was felt that cortisone might be effective in this in the same modus operandi as it has effected other collagenous diseases. The failure to influence the condition by local infiltration stimulated its trail by systemic means, the drug being administered either intramuscularly or orally (94).

B. Methods and Results:

In one patient, cortisone was administered intramuscularly for two weeks and in another orally for three weeks. Biopsies, photographs and plaster casts were taken before and after treatment. In case 3, treated intramuscularly, the tips of the little and ring finger on the right hand both lacked one half centimeter of full extension and large nodules were present in the palm. The fingers of the left hand could be completely extended and a few small nodules were present. He had not noticed these changes in the right hand until six months previously or in the left hand until one month before admission. A biopsy was taken and a single injection of 200 mg. of cortisone was given daily for two weeks. Fasciectomy was then performed on the left hand.

Neither symptomatic nor clinically observable improvement was noted in the hands as a result of systemic cortisone therapy in 2 patients. Comparison of the pre-treatment biopsy and the palmar fascia removed at operation failed to reveal any significant changes (Fig.38).

In case 2:, treated orally, the tips of the little and ring fingers of the left hand lacked one and two cm. of extension respectively and nodules were present in the palm. The right hand showed minimal changes in the palm without contracture of the fingers. ^Changes in the hands characteristic of Dupuytren's Contracture had been observed by the patient for five years. Joint swelling and pain on movement of the fingers suggestive of rheumatoid arthritis had been present for four years.

In this patient prior to administration of cortisone a biopsy of the contracted palmar fascia of the left hand was taken and a total dose of 200 mg. of cortisone was given daily



Fig. 38. Systemic therapy with 200 mg. of cortisone daily for 14 days intramuscularly preoperatively. This shows typical whorls of active fibroblasts with some older less cellular fibrous tissue at lower left. No significant difference from control seen. by mouth in four equally divided doses for three weeks. At the end of this period fasciectomy was performed.

Results:

There was marked improvement in the rheumatoid arthritis manifested by decrease in size of the swollen joints and relief of pain on movement of fingers. On clinical examination, no improvement could be observed in the hypertrophied palmar fascia. It was assumed that the increase in range of movement of the left hand was due primarily to improvement in the arthritic condition and not to change in the palmar fascia. Biopsy taken after cortisone therapy showed no obvious change.

C. <u>Discussion</u>:

Under the conditions of this study, it seems to be apparent that local or systemic therapy with cortisone does not cause improvement in Dupuytren's Contracture of the hands. Of course, complete fasciectomy usually will relieve the condition, but a considerable percentage of patients experience a rather prolonged convalescence following operation. Those with a history of arthritis undergoing operations on the hand are particularly susceptible to post-operative stiffness of joints. As a logical development of this problem it was decided to employ cortisone following fasciectomy. Under these circumstances there is complete removal of the hypertrophic palmar fascia leaving a wound of considerable extent beneath the skin

flaps, which heals by the usual method of granulation tissue formation. An ever increasing volume of clinical and experimental research supports the hypothesis that cortisone may delay the formation of all elements of granulation tissue. It should be noted that treatment early in the stage of granulation tissue formation is thought to be more effective, just as acute systemic collagen diseases usually respond more readily than do many chronic collagen diseases after formation of scar tissue. Therefore, it was hoped that postoperative complications due to formation of scar tissue as well as stiffness and limitation of mobility of joints would be reduced.

Operation followed by systemic therapy.

A. Methods:

By administration of this hormone at varying periods following fasciectomy it was possible to observe its effect on formation of adhesions and stiffening of joints. In two patients therapy was started immediately postoperatively with doses of 200 mg. daily. Another, received 100 mg. daily commencing on the seventh postoperative day while the fourth case received cortisone as an adjunct to physiotherapy three and a half months after operation.

B. Results:

Case l:

J.J. aged 40. Both hands of this white male were involved in Dupuytren's Contracture. His father, uncle and two siblings had the same condition. Involvement of the right hand was first observed ten years before admission. The ring finger lacked one half cm. of complete extension and the distal part of the palm was involved. Changes began in the left hand six years before admission, but progressed more rapidly so that both little and ring fingers lacked one cm. of full extension. Large nodules of hypertrophic scar tissue were situated in the distal part of the palm over the fourth and fifth metacarpals and proximal phalanx of the little finger. Immediately after operation on the right hand he was started on 200 mg. of cortisone orally in four equally divided doses daily. Three days later, fasciectomy was performed on the left hand and therapy continued as before until sixteen days after the second operation.

The appearance of the hands preoperatively is shown in Fig.39 and the free range of movement on the tenth and thirteenth day postoperatively is seen in Figs. 40 and 41. This range of movement did not cause discomfort or separation of the wound edges.

Case 2:

H.S. aged 48. Both hands of this white male were involved



Fig. 39, Case 1 : Plaster models of the hands show the extent of involvement, mainly in the palms without much contracture.



Fig. 40 left, and 41 right, Case 1 : Operation followed by cortisone therapy. Complete flexion and extension was possible at 10 days (left hand) and 13 days (right hand) postoperatively.

with Dupuytren's Contracture, the right very slightly and the left more extensively. Family history was non-contributory. The extent of involvement of the hands is described under case 2 receiving systemic administration. This patient had suffered from rheumatoid arthritis affecting the hands and right wrist for the past four years. The disease started in the left hand first and the fingers were quite deformed. No other joints have been involved. He first noticed firm nodules forming in the palm of the left hand five years ago and shortly afterward in the right palm. The left hand became progressively worse but the right hand was only slightly involved. Immediately following fasciectomy, oral cortisone in dosage of 200 mg. daily was continued for two weeks postoperatively and then was gradually discontinued. It should be recalled that this patient had also received the same dosage for three weeks prior to operation.

This patient was one in whom a prolonged period of postoperative stiffness of the hand might be anticipated because of the extensive degree of involvement of the hands by rheumatoid arthritis. In spite of the apparently poor prognosis a wide range of movement of the fingers without pain was obtained by the fifteenth day, and union of the wound margins had occurred.

Case 3:

G.P., aged 42. The family history was negative for

Dupuytren's Contracture. The little and ring fingers of the right hand could not be completely extended, each of these fingers lacking about one half cm. of full extension (Fig. 42). In addition, large nodules and scar bands were present over the distal half of the fourth and fifth metacarpals and first phalanx of the little finger. He claimed that the first appearance of the condition had started about seven months previously. A fasciectomy was performed. One week postoperatively parenteral injection of 100 mg. of cortisone was given for two weeks. Two weeks after operation complete flexion, with the exception of the little finger which lacked one half cm. of flexion and a range of almost complete extension was obtained (Figs. 43 and 44). On the twenty-third day a complete range of movement and firm grip was present. To summarize, then this patient, with only moderate involvement of short duration, obtained a rapid return of complete functional movement which quite probably might have occurred without hormone therapy.

Case 4:

R.A., aged 45. Both hands of this white female were involved by Dupuytren's contracture, the right ring and little finger lacking one half and one cm. respectively of full extension, with firm cords and nodules in the vicinity of the distal flexion crease. The condition had been present for about six months.



Fig. 42, Case 2: The extent of the flexion of the fingers and the appearance of the nodules can be seen.



Fig. 43, and 44, Case 3: Operation followed by cortisone therapy. These demonstrate that there is almost a complete range of motion at 14 days postoperatively. Nine days later extension was complete and a firm grip present.

The family history revealed a strong hereditary predisposition, since the patient's maternal grandfather, father and two brothers had become similarly affected. A fasciectomy was performed by another surgeon. Following operation there was some delay in healing of the skin incision which probably stimulated the development of excess scar tissue in the palm with subsequent limitation of extension of the little, ring and middle fingers. Seven weeks postoperatively, intermittent elastic traction splinting of the hand was carried out for three weeks. Upon discontinuing the use of this splint the fingers contracted markedly. Nine weeks postoperatively 400 mg. of vitamin E was given daily for one month, and since no improvement occurred as a result of this therapy 15 mgm. of desoxycorticosterone acetate and 300 mgm. of vitamin C were given daily for one week, without benefit.

Three and a half months after operation the patient was admitted to the Royal Victoria Hospital. The maximum amount of extension of the middle, ring and index fingers, which could be obtained is shown in Fig. 45. There was dense scarring in the region of the incision on the hypothenar eminence and along the distal flexion crease of the midpalm. Beginning on May 11th, cortisone acetate was administered intramuscularly in doses of 100 mgm. daily for one week. The dose was then increased to 200 mgm. daily for another week because the eosinophil count had not shown any adequate drop. Physiotherapy, consisting of whirlpool baths and massage, was started



Fig. 45, Case 4: Maximum extension at time of admission to hospital $3\frac{1}{2}$ months after first operation.



Fig. 46, Case 4: Cortisone as an adjunct to other therapy. The marked improvement in extension following 2 weeks of cortisone therapy may be noted.



Fig. 47, Case 4: Maximum extension one month after cessation of hormone therapy. Further improvement is shown despite discontinuance of drug. Follow up one year later showed almost complete flexion and extension of all fingers. on May 13th, and five days later an elastic extension splint was applied. During the two-week period of cortisone therapy there was marked improvement in the degree of extension of the little, ring and middle fingers (Fig.46). The systemic manifestations were as follows: the eosinophils decreased to 10 at the conclusion of treatment and there was an increase in body weight of 5 pounds.

During the two-month period prior to cortisone therapy, elastic extension splinting had been used for several weeks without visible improvement. Therefore, it was considered that the addition of cortisone therapy to physiotherapy and active splinting, largely contributed to the rapid improvement which took place during the two-week period. One month after cessation of hormone treatment the degree of extension of the fingers had improved still further (Fig. 47). One year later the range of movement was again increased. The clinical data and timing of the various types of treatment are summarized in Fig. 48.

C. <u>Discussion</u>:

In one case hormone therapy was delayed until one week postoperatively, but subsequent experience in these cases shows that even with early therapy, epithelial union is not delayed to an extent which would precipitate the risk of separation of the wound edges. As a precaution the stainless steel sutures may be left in for two weeks or more if necessary. Parenteral



Fig. 48, Case 4: The timing and sequence of various treatments employed is shown in the above chart. It is apparent that the increased range of motion is correlated to the administration of cortisone. injection of cortisone acetate was employed at first but was superseded by cortisone tablets.

A fall in the level of the circulating eosinophils is commonly used as an index in treatment of patients with cortisone. It cannot be stated with certainty that when a fall of eosinophils occurs that a dose adequate for the treatment of the condition concerned has been attained. However, it is the most convenient method available at present and a marked fall does indicate the dose of cortisone has had some effect. Oral administration, three or four times daily, has many advantages including: freedom from painful injections, rapid absorption and rapid action. There is freedom from prolonged effect should dangerous reactions occur. The effective oral dose is similar to that usually given intramuscularly.

Hormone therapy should be withdrawn gradually for several reasons. Administration of cortisone inhibits the output of endogenous corticotropin by the pituitary gland and as a result there is some degree of adrenal cortical atrophy which requires a week or ten days to overcome. It is possible that sudden complete withdrawal may cause stiffness of joints of the hand, and oedema, particularly if there has been a history of rheumatoid arthritis.

A history of active peptic ulcer, previous psychotic state or tuberculosis should exclude treatment with ACTH or cortisone.

Since it is difficult to find patients who exhibit the same degree of involvement with Dupuytren's Contracture of both hands, on whom a controlled study may be carried out, it is obvious that a large number of cases must be treated by fasciectomy and hormone before statistical improvement in result over fasciectomy alone can be proved. While only a limited number of cases have been treated, it appears that local injection and even systemic therapy without operation offers little promise. However, in six patients, combination of operation and hormone therapy seemed to facilitate the early return of a free range of extension and flexion. Perhaps the greatest practical use of hormone therapy in Dupuytren's Contracture will be for those in whom for one reason or another stiffness of joints may be anticipated postoperatively.

BIBLIOGRAPHY.

- 1. Hench, P.S., Kendall, E.C., Slocumb, C.H., and Polley, H.F. The effect of a hormone of the adrenal cortex (17 hydroxy-ll-dehydrocorticosterone, compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc. Staff. Meet. Mayo Clinic 24:181, 1949.
- 2. Mason, H.L., Myers, C.S., and Kendall, E.C. Chemistry of crystalline substances isolated from suprarenal gland. J. Biol. Chem. 114:613, 1936.
- 3. Sarett, L.H. Partial synthesis of Pregnene-4-triol-17(B). J. Biol. Chem. 162:601, 1946.
- 4. Hench, P.S., Kendall, E.C., Slocumb, C.H., and Polley H.F. Effects of Cortisone Acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. Arch. Int. Med. 85:545, 1950.
- 5. Smith, P.E. Hypophysectomy and a replacement therapy in the rat. Am. J. Anat. 45:205-274, 1930.
- Li, C.H., Simpson, M.E., and Evans, H.M. Isolation of ACTH from sheep pituitaries. Science 96:450, 1942.
- 7. Sayers, G., White, A., and Long C.N.H. Preparation of pituitary ACTH. Proc. Soc. Exp. Biol. and Med. 52:199, 1943.
- 8. Selye, Hans. Text book of endocrinology, 2nd Ed.; 1949. Acta Endocrinologica, Inc., Montreal, Canada.
- 9. Trepat, L., and Petre, A.J. Pallida universal for shock emotivo. Semana Medica, 1:65, 1942.
- 10. Brozek, J.S., Wells, S., and Keys, A. Med. aspects of semi-starvation in Leningrad. Am. Review of Soviet Med. 4:70, 1946.

- 11. Li, C.H., Simpson, M. and Evans, H. Influence of ACTH and growth hormone on body composition of hypophysectomized rats, summarized. Endocrinology 44:71, Jan. 1949.
- 12. Snow, J.S., and Whitehead, R.W. Relationship of the hypophysis to hair growth in the albino rat. Endocrinclogy 19:88-96, Jan. Feb. 1935.
- Selye, H. Unpublished Data 35935 N.D.
- 14. Houssay, A.E., and Higgins, G. The effect of gonadectomy on the growth of hair in mice. Proc. Staff Meeting of Mayo Clinic 24:269, May 1949.
- 15. Baker, B.L., and Whitaker, W.L. Interference with wound healing by the local action of adrenocortical steroids. Endocrinology 46:544, 1950.
- 16. Furuya, Kiyoshi Experimentelle Untersuchungen uber den einfluss der drusen mit innerer sekection auf die Wachstumsvorgange. Biochem, Ztachr. 147:425, 1924.
- 17. Chang, H.C. Specific influence of the thyroid gland on hair growth. Am. J. Physiol 77:562:567, August 1926.
- 13. Chang, H.C., and Feng, T.P. Further studies on thyroid - hair growth. Chinese J. Physiol. 3:57:68, Jan. 1929.
- 19. Butcher, E.O. The effects of irritants and thyroxin on hair growth in albino rats. Am. J. Physiol 129:553-559, June 1940.
- 20. Butcher, E.C. Hair growth in adrenalectomized, and adrenalectomized thyroxin treated animals. Am. J. Physiol 120:427-434, Nov. 1937.
- 21. Freud, J. Hypophysis and hair. Acta brev. Neerland 4:99-100, 1934.

- 22. Snow, J.S., and Whitehead, R.W. Relationship of the hypophysis to hair growth in the albino rat. Endocrinology 19:88-96, Jan. Feb. 1935.
- 23. Kylin, Eskil Om. hypotysens betydelse for harbildnigen och narets tillvaxt. Svenska Lak - Tidning 35-1687, Oct. 1938.
- 24. Butcher, E.O., and Richards, R.A. The relation of the adrenals to the retarded hair growth in underfed albino rats. Endocrinology 25:787-792, Nov. 1939.
- 25. Whitaker, W.L., and Baker, B.L. Inhibition of hair growth by the percutaneous application of certain adrenal cortical preparations. Science 108-206, August 1948.
- 26. Ralli, Elaine P., and Graef, Irving. Stimulating effect of adrenalectomy on hair growth and melanin deposition in black rats. Endocrinology 32: 1-12, January 1943.
- 27. Forbes, Thomas, R. Hormones and hair changes in rats. Endocrinology 30:465, Mar. 1942.
- 28. Hooker, C.W. and Pfeiffer, W. Effects of sex hormone on body growth skin, hair and sebacceous glands in the rat. Endocrinology 32:-69 Jan. 1943.
- 29. Von Wattenweil, H. Die wirkung subkutan implantierter Aestradialtableten auf das Haarklied des Meerschweinchens. Schweiz Med. Wchnschr 71:1331, 1941.
- 30. Gardner, W.V., and De Vita, J. Inhibition of hair growth in dogs receiving estrogens. Yale J. Biol. & Med. 13:213, 1940.
- 31. Williams, W.L., Gardner, W.V., & De Vita, J. Local inhibition of hair growth in dogs by percutaneous application of estrone. Endocrinology 38:368, 1946.
- 32. Hooker, C.W. and Pfeiffer, W. Same as (28).

33. Halban, Josef. Ueber ein büschen nicht beachtetes Schwangerschafts symptom. Wüchn Klin Wchnscher 19:6, 1906.

34. Dawson, Helen L. On hair growth. Am. J. Anat. 53:89, 1933.

- 35. Hensel, Georg. Corpus luteum - hormon und haarwachstum. Ztschr. F.D. ges exper. Med. 104:182, 1938.
- 36. Dawson, Helen L. On hair growth. Am. J. Anat. 53:89, 1933.
- 37. Houssay, A.B., and Higgins, G.M. The effect of gonadectomy on the growth of hair in mice. Proc. Staff Meeting, Mayo Clinic 24:269-275, 1949.
- 38. Houssay, A.B., and Higgins, G.M. The effect of gonadectomy on the growth of hair in mice. Proc. Staff Meeting of Mayo Clinic 24:269, May 1949.
- 39. Forbes, T.R. Sex hormones and hair changes in rats. Endocrinology 30:465, 1942.
- 40. Baker, Burton L., Dwight J.Ingle, Choh, H.L., and Evans, Herbert M. Growth inhibition in the skin induced by parenteral administration of adrenocorticotropin. Anat. Rec. 102:3, 1948.
- 41. Snow, J.S., and Whitehead, R.W. Relationship of the hypophysis to hair growth in the albino rat. Endocrinology 19:88-96, Jan.Feb. 1935.
- 42. Baker, B.L. Personal Communication Feb. 22, 1950.
- 43. Baker, B.L. Same as (40).
- 44. Same as 41.

94

45. Mote, John R. Proceedings of the second clinical ACTH Conference The Blakistan Co. Phil. 1951.

مدر د. دا است. د ادرو**ا میده بومی با**ید اید افزیش ا دا از این

- 46. Ragan, Charles, Grokoest, A., Boots, R.A.
 Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis.
 Am. J. of Med. Vol. VII 6:741-750, 1949.
- 47. Whitelaw, M.J. Physiological reaction to pituitary adrenocorticotrophic hormone (ACTH) in severe burns. J.A.M.A. 145:85, 1951.
- 48. Baker, B.L., and Whitaker, W.L. Interference with wound healing by the local action of adrenocortical steroids. Endocrinology 46:544, 1950.
- 49. Baker, B.L. and Coster, C.W. Cutaneous atrophy induced by local treatment with adrenocortical steroids. Anat. Rec. 106:173, 1950.
- 50. Spies, T.D., Stone, R.E. Birmingham Alabama. The effect of the local application of synthetic cortisone acetate on the lesions of iritis and uveitis of allergic dermatitis and of psoriasis. Southern Med. J. Vol. 43, 43:871-874, 1950.
- 51. Leopold, I.H. Local and systemic cortisone in ocular disease. Am. J. Ophth. 34:361, 1951.
- 52. Woods, Alan C. Clinical and experimental observation on the use of ACTH and cortisone in ocular inflammatory disease. Am. Jour. Ophth. 33:9, 1950.
- 53. Jones, J.S., Meyer, K.

Inhibition of vascularization of the rabbit cornea by local application of cortisone. 12th Annual Staff Meeting Inst. of Ophthal. Presbyterian Hospital New York, April 1950.

- 54. Hollander, J.L., Brown, E.M., Jessar, R.A., and Brown, C.Y. Hydrocortisone and cortisone injected into arthritic joints. J.A.M.A. 147:1629, 1951.
- 55. Baker, B.L. and Whitaker, W.L. Interference with wound healing by the local action of adrenocortical steroids. Endocrinology 46:544, 1950.

56. Baker, B.L. and Coster, C.W. Cutaneous atrophy induced by local treatment with adrenocortical steroids. Anat. Rec. 106:173, 1950.

- 57. Conway, Herbert, and Stark, R.B. ACTH in plastic Surgery. Plastic and reconstruction surgery. 8:354, 1951.
- 58. Ragan, C., Howes, E.L., Plotz, C.M., Meyer, K., Blunt, J.W. Effect of cortisone on production of granulation tissue in the rabbit. Proc. Soc. Exper. Biol. & Med. 72:718, 1949.
- 59. Ragan, C., Howes, E.L., Plotz, C.M., Meyer, K., Blunt, J.W. and Lattes, R. The effect of ACTH and cortisone on connective tissues. Bull. New York Acad. Med. 26:251, 1950.
- 60. Blunt, J.W., Plotz, C.M., Lattes, R., Howes, E.L., Meyer, K., and Ragan, C. Effect of cortisone on experimental fractures in rabbit. Proc. Soc. Exper. Biol. & Med. 73:678, 1950.
- 61. Plotz, C.M., Howes, E.L., Meyer, K., Blunt, J.W. Lattes, R., and Ragan, C. The effect of the hyperadrenal state on connective tissue. Am. J. Path. 26:709, 1950.
- Spain, D.M., Molomut, W., and Haber A. The effect of cortisone on the formation of granulation tissue in mice. Am. J. Path. 26:710, 1950.
- 63. Baker, B.L., Ingle, D.W., Li, C.H., and Evan, H. Growth inhibition in the skin induced by the parenteral administration of adrenocorticotropin. Anat. Rec. 102:313, 1948.
- 64. Green, H.N. Suggested mode of action in corticotropin in rheumatoid arthritis and the allergic state. Brit. M.J. 2:1165, 1950.
- 65. Hench, P.S., Kendall, E.C., Slocumb, C.H., Polley, H.F. The effect of a hormone of the adrenal cortex (17hydroxy-ll-dehydrocorticosterom: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff. Meet. Mayo Clin 24:181-198, 1949.

- 66. Hench, P.S., Kendall, E.C., Slocumb, C.H., Polley, H.F. The effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. Arch. Int. Med. 85:545-566, 1960.
- 67. Ragan, C., Grokoest, A.W., and Boots, R.H. Effect of adrenocorticotropic hormone (ACTH) on rheumatoid arthritis. Am. J. Med. 7:741-750, 1950.
- 68. Creditor, M.D., Bevans, M., Mundy, W.L., and Ragan, C. Effect of ACTH on wound healing in humans. Proc. Soc. Exper. Biol. & Med. 74:245-247, 1950.
- 69. Thorn, G.W., Forsham, P.H., Frawley, T.F., Hill, S.R., Roche, M., Strachelin, D., and Wilson, D.L. Clinical usefulness of ACTH and cortisone. New England J. Med. 242:783-793, 1950.
- 70. Beck, J.C., Browne, J.S.L., Johnson, L.G., Kennedy, B.J. and MacKenzie, D.W. Occurrence of peritonitis during ACTH administration. Canad. M.A.J. 62:423-426, 1950.
- 71. Selye, H., Further studies concerning the participation of the adrenal cortex in the pathogenesis of arthritis. Brit. M.J. 2:1129-1135, 1949.
- 72. Venning, E. To be published.
- 73. Baker, B.L., Dwight, J.I., Li., C.H., and Evans, H.M. Growth inhibition in the skin induced by parenteral administration of adrenocorticotropin. Anat. Rec. 102: 313-332, 1948.
- 74. Davis, J.S. Skin transplantation. J. Hopk. Hosp. Reports, 15:307, 1910.
- 75. Davis, J.S. Some of the problems of Plastic Surgery. Am. Surg. 66:89, 1917.
- 76. Davis, J.S. Transplantation of skin. Surg. Gyn. Obst. 44:181, 1927.

- 77. Minervini, R. On the practical value of free grafting of the skin of the factus and new born. 17th Internat. Congress of Med. London, 1913.
- 78. Kubanyi, A. Blood grouping as a guide for skin grafting. Arch. Klin. Chir. 129:644, 1924.
- 79. Ashley, F. Foreskins as skin grafts. Am. Surg. 106:252, 1937.

- 80. Shimkin, N.I. Two rare cases of homoplastic surgery of eyelids. Brit. Jnl. Ophthal. 29:424, 1945.
- 81. Mandl, F., and Rabinovici, N. Microscopically verified case of pinch homografting in human case. Jnl. Internat. Coll. Surg. 9:439, 1946.
- 82. Elschnig, A. cited by Spaeth, E.C., and Cappriotti, O.A. Heteroplastic and isoplastic skin grafts. Plastic and Reconst. Surg. 3:707, 1948.
- 83. Kearns, J.E., and Reid, S.E. Successful Homotransplantation of skin from parents to son. Plastic and Reconstr. Surg. 4:502, 1949.
- 84. Spaeth, E.B. and Capriotti, O.A. Heteroplastic and Isoplastic skin grafts. Plastic and Reconstr. Surg. 3:707, 1948.
- 85. Bauer, K.H. Homoiotransplantation von epidermis bei eineiigen zwillingen. Bertrs. Klin. Chir. 141:442, 1927.
- 86. Padgett, E.C. Is Iso-skin grafting prectical. South Med. Jnl. 25:895, 1932.
- 87, Brown, J.B. Homografting of skin with report of case in identical twins. Surgery 1:559, 1937.

- 88. Schattner, A. Report of Isograft transplants in identical twins. Arch. Otolaryng. 39:512, 1944.
- 89. Converse, J.M., and Duchet, G. Successful Homologous skin grafting in a war burn using an identical twin as a donor. Plastic and Reconstr. Surg. 2:342, 1947.
- 90. Rogers, B.O. The problem of skin homografts. Plastic and Reconstr. Surg. 5:269, 1950.
- 91. Medawar, P.B. Behavior and fate of skin homografts and isografts in rabbits. Jnl. Anat. 78: 176, 1944.
- 92. Baxter, Hamilton and Entin, M.A. Clinical study of the effects of homografts in man. Am. Jnl. Surg. 81: 285-294, 1951.
- 93. Bunnell, Sterling, Surgery of the Hand, Second Edition. J.B. Lippincott Co., Phila. 1948.
- 94. Freyberg, R.H., Traeger, C.T., Adams, C.H., Kuscu, T., Wainardi, H., and Bonomo, I. Effectiveness of Cortisone administered orally. Science 112:429, 1950.