THE AETIOLOGY OF KELOIDS: A REVIEW OF THE LITERATURE AND A NEW HYPOTHESIS*

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Keloid formation has probably been known to man for as long as trauma has occurred, but why certain people should develop keloids and others not, is unknown. This paper deals with a review of the literature on the aetiology of keloids, and a new idea on a possible mechanism predisposing to keloid formation is advanced.

Origin of the Term—Keloid

The first clear description of a keloid was given by Alibert[1] in 1806. He termed the lesions 'les cancroides'. In 1817 he introduced the name *cheloides* (from $\chi\eta\lambda\eta$—a crab's claw) because of the resemblance the lesion had to a 'shell-fish with processes like legs implanted into the skin'. In 1854 the term keloid ($\kappa\eta\lambda\iota\sigma$—a mark or blemish) was introduced by Addison,[2] although the lesions he described were certainly scleroderma.[3, 4] At that time 2 types of keloid were described, viz. the spontaneous, or true keloid, and the cicatricial keloid. Today, however, it is recognized that the so-called spontaneous keloid results from some minor or forgotten traumatic episode.

Definition and Pathology

Keloids are defined as benign, proliferative, fibrous outgrowths, having their origin in the subpapillary layer of the dermis, and develop as a result of trauma in certain predisposed individuals.

The keloid is localized to the reticular layer of the corium as a poorly circumscribed mass of connective tissue composed of interlacing bundles of hyalinized collagen. In the early stages there is moderate vascularization, giving the red colour to the keloid, as well as evidence of connective tissue mitosis. At a later stage the tissue is white, firm and relatively avascular.

Macroscopically the keloid is a type of hypertrophic scar with a rounded, shiny surface, and it often has a bizarre shape. It is steeply elevated above the skin surface, exceeding the traumatized area, and extending deep into the dermis. It itches, in its early stages, and very rarely regresses spontaneously. The tendency for local recurrence after surgical removal is well known.

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Histologically, the keloid is composed of thick, homogeneously eosinophilic bands of collagen admixed with thin collagenous fibres and large, active fibroblasts. The epidermis is flattened and becomes atrophic as do the appendages of the skin.

X-ray diffraction examination of normal skin has shown that there are two systems of collagen fibrils in the dermis, the main system running parallel to the skin-crease lines and the other running perpendicular to it. In a mature scar the collagen fibrils always run parallel to the line of the scar, whereas in a hypertrophic scar this orientation is slight. In a keloid there is no orientation of the collagen at all.[5]

REVIEW OF THE LITERATURE

Many constitutional factors have been cited, in the literature, as predisposing to keloid formation. These have been listed as follows:

A. *Trauma*

In the vast majority of cases trauma has been the main, if not the only, provoking factor in keloid formation. The trauma may be in any form from an insect bite to a major burn. Vaccinia, acne, smallpox and herpes zoster are frequent causes, as are sites of injections. That trauma is the sole aetiologic factor in keloid formation has long been discounted, as keloid is an uncommon sequel to trauma to the skin. Because of this, most writers in this field have subscribed to an underlying predisposing factor.[6-15]

B. *Increased Skin Tension*

One experimenter found that when he repeatedly injected his own serum intracutaneously he produced a large fibromatous area.[16] Microscopic evidence showed subepithelial changes similar to those seen in keloids. These experiments were carried out because of the fact that keloidosis was found to be related to skin oedema and that with decrease in the local transudate there resulted a shrinking of the keloid.[7] This theory is unable to explain the greater incidence of keloids in the Negro.

It has been found with long-standing oedema that the mucopolysaccharide content in the skin is maintained at a high level and this stimulates the deposition of collagen fibrils, thus causing a fibrous organization to take place.[9] However, what determines the tumour-like growth and regrowth of keloids remains unexplained.

C. *Foreign-body Reaction*

Some authors[14] found that in 70 cases of keloids the scar hypertrophy was due to a peculiar, spreading, proliferative

process elicited in sensitive people locally by the presence of various particles acting as foreign bodies. They considered the tumours to be some sort of foreign body granuloma. It was found that keratin could set up this reaction. The fact was also stressed, however, that production of the lesion also depends on systemic factors, with which other authors also agree.

D. *General Causes*

1. *Age.* Generally, children and young people in the age of growth have the highest incidence of keloid formation.[6, 9-13, 18] In one series, the major percentage of keloids occurred in the second decade (23 out of 67 patients). 58 of these patients were between 0 and 30 years old.[6] One writer thought that this was due to the greater incidence of trauma in the younger age group,[17] but most authors agree that keloids are uncommon in later life.

2. *Race.* Keloids are more common, by far, in the Negroes,[6, 7-11, 15, 17, 19, 20] with the Hindus, Malayans[21] and other Coloured races also showing a marked predisposition. Various authors have found the ratio of Negroes to Whites as 2:1,[19] 19:1,[22] 14:1,[23] and 9:1.[24] In a recent survey, 74% of 247 patients were Negro.[3]

This has been thought to be due to the fact that black races have a fibroplastic predisposition (this includes the tendency to form fibroids, adhesions, etc.),[8, 9, 15, 19, 25] but this view is not generally accepted.[3, 7] One author has tried to explain this keloid diathesis in Negroes on the lines of Darwin's theory of sexual selection,[15] and yet another has thought this due to the practice of tribal scarification in Africa, Polynesia, Australia, etc.[26] This latter theory does not explain the high incidence in the American Negro.

In South Africa, the Bantu have a far greater incidence of keloid formation than the White.[13]

3. *Sex.* Some observers have found the sexes to be equally affected,[12, 18] while others have found that females predominate.[3, 10] One author found the ratio of females to males as 2·2:1.[3] This may be due to the fact that the female is more conscious of the cosmetic effect of the keloid and therefore goes to her physician more readily than a male would.

4. *Familial.* Many examples of keloids occurring in families have been quoted in the literature.[27-30] One author has described keloids on the sternal region of 3 generations of one family,[10] while another writer has reported a case of congenital keloids.[31] This tendency to keloid formation in families has been thought to be due to a hereditary physicochemical difference in the individual subject which results in an overproduction of connective tissue at the sites of injury, and has been called a fibroplastic diathesis.[15]

The percentage of hereditary cases is too low, however, to be of any major significance.

5. *Skin contents.* Not only have keloids been found to be more common in Negroes, but also in people of all races with a deeply pigmented, swarthy, oily skin, as compared to those with a light, thin, dry skin. The White peoples stemming from the Mediterranean areas, who have the dark, oily, heavy skins, are more prone to this condition than the fair peoples of the Northern European areas. This was thought to be due to the darker skins having a higher sulphur content than fair skins.[17]

E. *Infections*

1. *Tuberculosis.* The opinion was once held that keloids are caused by the tubercle bacillus.[18, 33] Subsequent workers experimented by injecting ground-up keloid tissue into guinea-pigs and observing these animals.[34, 35] No local or general lesions were noted. Serologic tests with antigen extracted from keloid tissue also gave negative results as to the tuberculous element. In a later series of 168 patients with keloids, not one was found to have clinical evidence of tuberculosis, and the number of positive tuberculin reactions was in the range of the normal population.[6]

2. *Syphilis.* This was similarly thought to promote keloid growth, but in a subsequent series of 248 cases of keloid, only one patient with syphilis was found.[6]

F. *Endocrine Causes*

1. *Thymus.* One of the workers in this field found residues of the thymus in several of his patients with keloids. He attributed the keloid formation to factors in the thymus.[36]

2. *Parathyroid.* Hypercalcaemia was found in 75% of one series of cases and a constant increase of calcium salts was found in all the keloid tissue.[36] This led to the belief that keloid formation resulted from hyperparathyroidism. Subsequent workers found that this was not true, and that the blood calcium, in most keloid cases, is within normal limits.[6]

3. *Ovary.* A possible association of keloids to ovarian function has been stressed because of their presence at puberty, spontaneous resolution after the menopause, and their appearance or increase in size during pregnancy.[6, 13, 32, 36] One author described keloids that developed during pregnancy in scars that were 4 years old.[10]

Some observers thought that there was a greater content of oestrogen in keloids,[37] but it was subsequently found that depression of the ovaries did not alter the course of the keloid.[12]

4. *Thyroid.* At one time there was a strong belief that thyroid function was tied up with keloid growth. One writer claimed that he induced keloids in hyperthyroid patients by irritating their skin 'with excitant pharmacologic substances, the activity of which was slight'.[38] Others reported that hard fibrous patches (? keloids) in a woman patient regressed following a unilateral resection of the thyroid gland on that side[39] and yet others noted that keloids were formed following the injection of thyroid extract after thyroidectomy.[40] It has been recorded that young patients thyroidectomized for Grave's disease are apt to form keloids in the operation wound.[9]

5. *Pituitary.* It has been stated that the predisposition to keloid formation seems to bear a pathognomonic relation to the hypothalamus and hypophysis. Acromegalics have been reported as having a marked susceptibility to the development of keloids.[9, 41] This has been thought to be due to the action of growth hormone, which stimulates the new formation of connective tissue, especially the formation and deposition of collagen fibrils, and thyrotrophic hormone (TSH), which stimulates the synthesis and cellular release of mucopolysaccharides to the ground substance, influencing the tissue cells directly and not by way of the thyroid gland.[41] The influence of adrenocorticotrophic hormone and melanocyte-stimulating hormone on the skin is known but has not, as yet, been tied up with keloid formation.

6. *General.* Garb and Stone,[6] in their survey, subscribed to the theory of hormonal stimulation as being the main or important contributing cause of keloid formation. In support of this they quote the fact that 34% of their 248 patients were at puberty, the age of most hormonal activity. Their theory has been supported by the observations of other writers in that keloids are predominant in young people, during their years of growth, and in pregnant women.[9, 10, 12, 13] It has also been noted that keloids tend to regress spontaneously after the menopause and that they are rare in the aged.[9, 12, 13] Other authors have found that endocrine disturbances tend to increase the incidence of keloids.[4, 9]

Many workers in this field have concluded that some hormonal factor plays the main aetiologic role in keloid formation, with trauma being the provoking factor.[4, 6, 9, 10, 12, 13, 34, 35, 38-40]

G. *Main Sites of Keloid Formation*

No part of the body is exempt from keloid formation, but they are more common over the neck, face, ear lobes, sternum and back of the chest.[3, 6-8, 10, 11, 32] It has been noted that no matter how great the tendency is for keloids to form, they very rarely appear on the hands or feet.[3, 17] In a recent survey of 340 lesions in 247 patients, 35% were on the ear lobes, 20% on the face and 16% on the neck, i.e. 71% were on the neck-face area, whereas only 0·6% were on the hands and feet.[3]

Some authors have felt that there is a difference in the susceptibility of various parts of the body to keloid formation, it being most likely to occur on the neck, ears and pre-sternal area.[8]

PIGMENT-CONTROLLING FACTORS OF THE SKIN

The colour of the human skin is caused by the pigment melanin ($\mu\epsilon\lambda\alpha\sigma$-black) which is produced from tyrosine in specialized cells called melanocytes. Melanocytes in the

human skin are sandwiched in a layer between the epidermis and the dermis. The number of melanocytes in peoples of different races, is the same. Colour differences are due to differences in distribution of melanin granules in the melanocytes.[42]

Melanocytes are formed from nerve tissue, and in the third month of foetal life they migrate to the skin, eyes, hair and coverings of the brain. They retain their dendritic shape.

It has been estimated that there are approximately 2 billion melanocytes, weighing 1 G as a group, in the human epidermis. Each cell can be regarded as a unicellular gland secreting, along its dendritic processes, melanin into its neighbouring epidermal cells. The melanin is light-brown in colour in reduced form, and dark-brown when oxidized, the latter being achieved by the photochemical effect of long-wave ultraviolet rays. The melanocytes have the capacity to convert tyrosine into dihydroxyphenylalanine (dopa) and dopaquinone by hydroxylation, and thence, by a series of intermediates, to melanoprotein. Melanin granules are thought to pass from melanocytes into epidermal cells by pinocytosis, i.e. the end of a dendritic process presses against the wall of an epidermal cell, and when the latter requires melanin it appears to phagocytose a part of the dendrite so that melanin particles flow into the cell.[45]

The face, neck, armpits and groin are the richest sources of melanocytes in the body, while the palms and soles are the poorest.

Naevi are clusters of melanocytes, whereas freckles have a smaller amount of melanocytes than normal skin, but these have a greater tyrosinase activity and are larger than normal melanocytes.[42, 45]

Melanin deposition by melanocytes is controlled by 2 hormones secreted by the middle lobe of the pituitary in animals.[42] In man these are secreted by the posterior part of the anterior lobe of the pituitary.[44] The hormones are α- and β-melanocyte-stimulating hormone (MSH). Both α- and β-MSH are polypeptides.[43] α-MSH has been found to be the same in pigs, cows, horses and monkeys and is thought to be the same in man. β-MSH differs from species to species.[42]

Melanocytes, in White and Coloured peoples, have the same amount of melanin. In the White people, the melanin is aggregated in the centre of the cell, whereas in the Coloured people it is uniformly dispersed throughout the cell. The action of MSH is to cause this dispersion. How this is brought about is unknown. MSH does not seem to influence the actual production of melanin.

In man, MSH has this darkening effect, which has been proved by the fact that ablation of the pituitary, whether by disease or therapeutic measures, results in depigmentation of the skin, and also administration of MSH to human subjects darkens the skin. This darkening is generalized, though deeper in exposed areas. If large doses of MSH are given to patients with hypopituitarism, the pigmentation appears within 2 days, while the skin returns to its previous pallor within a few weeks of giving the last dose.[44, 46]

It is now generally accepted that pigmentation, in man, is due to the pituitary secretion of MSH, though whether the fact that the Negro is so dark is due to a higher MSH output than that of the Caucasian, or whether his melanocytes are more sensitive to the hormone, is unknown.

Adrenocorticotrophic hormone (ACTH) has been found to have a similar effect on pigmentation as MSH. This is not surprising as the 13 amino acids of the α-MSH molecule are in the same sequence as the first 13 amino acids of the 39 amino-acid molecule of ACTH. This was thought to account entirely for the darkening of the skin in Addison's disease and pregnancy, but it is now accepted that hyperpigmentation in these conditions is due mainly to increased MSH. There appears to be a common mechanism controlling the secretions of MSH and ACTH.[44, 48]

It has recently been shown that large amounts of ACTH (2,400 units per day) can produce intense hyperpigmentation, but the proportionate role of ACTH, as compared to MSH, in human pigmentation is unknown.[46] The evidence obtained, so far, seems to point to MSH playing the major role.

The control of MSH secretion by the pituitary is obtained through a negative-feedback mechanism. The factors influencing the controlling processes are closely related to those affecting the control of ACTH secretion (Fig. 1). MSH and ACTH secretions thus go 'hand-in-

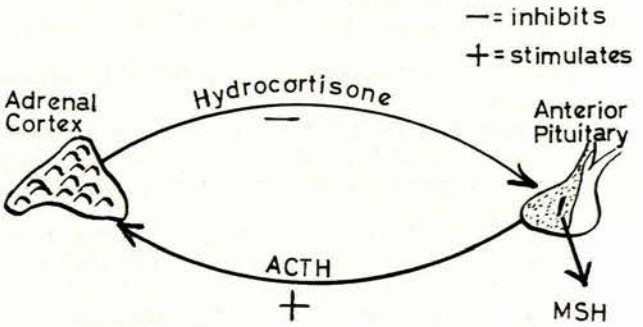

Fig. 1. See text.

hand'. Conditions causing increased ACTH secretion will therefore have the same effect on MSH secretion, e.g. pregnancy and Addison's disease.

From the diagram, it may be seen that the amount of hydrocortisone secreted is inversely proportional to that of MSH.

Sex hormones have been found to affect pigmentation in that they probably sensitize the skin to the action of MSH, and they determine, to some extent, the distribution of pigmentation.[44] It has been observed that many females tend to develop increased pigmentation around their mouth, eyes, face and nipples during their menses. This has been found to occur most commonly in the premenstrual week. It appears that the skin is more sensitive to ultraviolet light during this period, and it is thought that this is due to MSH.[47] Increased pigmentation in pregnancy is well known. It has also been found that treatment with testosterone, in castrates, causes increased pigmentation and tanning ability.[49] This also probably works through the pituitary.

Hyperpigmentation has been noted in cases of hyperthyroidism.[44] This pigmentation has been found to be diffuse or localized. The commonest situations are the palmar creases, scars or the periorbital regions. Certain

workers[50] have conducted experiments which have given them sufficient evidence to suggest that there is an increase in ACTH production in thyrotoxicosis. That ACTH is the sole cause of the pigmentation is not unlikely, but knowing that ACTH and MSH are under the same control, it is suggested that there is an increased secretion of MSH in hyperthyroidism.

A hormone, called melatonin, has been isolated from the pineal gland of mammals.[42] This hormone has been found to lighten melanocytes in animals, but seems to have no effect on human skin. It has been found that the secretion of melatonin, by the pineal, is controlled by the concentration of ultraviolet light, in that the greater the amount of ultraviolet rays present, the lower the secretion of melatonin, and vice versa.[51]

HYPOTHESIS

This review of the literature lends strong support to the theory that keloid formation is linked to an aberration of MSH metabolism.

The reasons for this association are as follows:

1. The high incidence of keloids in dark-skinned races, whose melanocytes are apparently more reactive to MSH.
2. The fact that deeply pigmented, swarthy skins, in people of all races, seem more prone to keloid formation than fair skins.
3. The relation of hyperpituitarism to keloid formation, as in acromegalics.
4. The fact that the incidence of keloids is higher in states of physiological hyperactivity of the pituitary, e.g. puberty and pregnancy, and that these are associated with increased pigmentation.
5. The fact that the main sites of keloid formation are on the parts of the body where the concentration of melanocytes is greatest, such as the face and neck, and that keloids are extremely rare on the palms and soles where the concentration of melanocytes is minimal.
6. The well-recorded relation of keloids to thyroid disease and the known increase of pigmentation in certain cases of hyperthyroidism.
7. A marked association of keloids to hydrocortisone.

Local injections of hydrocortisone[9, 12, 20, 52-55] and its derivatives such as 'kenalog' (triamcinolone acetonide),[57] 'decadron' (dexamethasone)[56] and 'depo-medrol', have all been used with a fair amount of success in treating keloids. It is now known that intradermal injections of triamcinolone are absorbed[58] and that hydrocortisone is an inhibitor of MSH output.

SUMMARY

From a review of the literature it has been established that:

1. Keloids are more common in dark-skinned people.
2. There appear to be hormonal factors involved in keloid formation, with trauma as the main provoking factor.

A new interpretation of the facts has been advanced, which postulates a relation between keloid formation and factors governing the control of pigmentation in the human skin. It is not known whether the important factor is an increase in MSH secretion, or a hypersensitivity of melanocytes to the effects of MSH.

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REFERENCES

1. Alibert, J. L. M. (1961): *Op. cit.*[3]
2. Addison, T. (1854): Med. Chir. Trans., **37**, 27.
3. Cosman, B., Crikelair, G. F., Ju, D. M. C., Gaulin, J. C. and Laffes, R. (1961): Plast. Reconstr. Surg., **27**, 335.
4. Van den Brenk, H. A. S. and Minty, C. C. J. (1960): Brit. J. Surg., **47**, 595.
5. Holmstrand, K., Longacre, J. J. and De Stefano, G. A. (1961): Plast. Reconstr. Surg., **27**, 597.
6. Garb, J. and Stone, M. J. (1942): Amer. J. Surg., **58**, 315.
7. Marshal, W. and Rosenthall, S. (1943): *Ibid.*, **62**, 348.
8. Trusler, M. M. and Bauer, T. B. (1948): Arch. Surg., **57**, 539.
9. Asboe-Hansen, G. (1960): Dermatologica (Basel), **120**, 178.
10. Jacobsson, F. (1948): Acta radiol. (Stockh.), **29**, 251.
11. Pfahler, G. E. and Keefer, G. P. (1948): Amer. J. Roentgenol., **59**, 378.
12. Solomons, B. (1952): Practitioner, **168**, 465.
13. Allan, J. C. and Keen, P. (1954): S. Afr. Med. J., **28**, 1034.
14. Glucksmann, A. (1951): Brit. J. Plast. Surg., **4**, 88.
15. Bohrod, M. G. (1937): Arch. Derm. Syph. (Chic.), **36**, 19.
16. Marshall, W. (1945): Amer. J. Surg., **69**, 338.
17. Kitlowski, E. A. (1955): Plast. Reconstr. Surg., **12**, 383.
18. Naegeli (1931): Bull. Soc. franç. Derm. Syph., **38**, 905.
19. Brenizer, A. G. (1915): Ann. Surg., **61**, 83.
20. Asboe-Hansen, G., Brodthagen, H. and Zachariae, L. (1956): Arch. Derm., **73**, 162.
21. Wooley, P. G. (1907): Amer. J. Derm., **11**, 481.
22. Fox, H. (1908): J. Cutan. Dis., **26**, 67.
23. Hazen, H. H. (1914): *Ibid.*, **32**, 705.
24. Matas, R (1937): *Op. cit.*[35]
25. Nason, L. H. (1942): New Engl. J. Med., **226**, 883.
26. Grosse, E. (1942): *Op. cit.*[6]
27. Gate, J. and Coste, J. (1931): Bull. Derm. Syph., **38**, 912.
28. Wilson and Hebra (1903): *Op. cit.*[36]
29. Schramek (1942): *Op cit.*[6]
30. Hutchinson, E. (1897): Edin. Med. J., **43**, 5.
31. Bryant and Rosenthal (1942): *Op. cit.*[6]
32. Saalfeld, E. and Saalfeld, U. (1942): *Ibid.*
33. Sabouraud, R. (1942): *Ibid.*
34. Pautrier, L. M. and Glasser, R. (1942): *Ibid.*
35. Marras, A. (1933): G. ital. Derm. Sif., **74**, 715.
36. Crocker, R. H. (1903): *Diseases of the Skin*, 3rd ed., p. 933. London: P. Blakiston.
37. Geschikter, C. F. and Lewis, D. (1935): Amer. J. Cancer, **25**, 630.
38. Justus, J (1919): Arch. Derm. Syph. (Berl.), **127**, 274.
39. Leriche and Jung (1942): *Op. cit.*[6]
40. Belassa (1942): *Ibid.*
41. Asboe-Hansen, G. (1959): Amer. J. Med., **26**, 470.
42. Lerner, A. B. (1961): Sci. Amer., **205**, 98.
43. Harper, H. A. (1961): *Review of Physiological Chemistry*, 8th ed., p. 362. Los Altos: Lange Medical Publications.
44. Annotation (1961): Brit. Med. J., **2**, 634.
45. MacKenna, R. M. B. (1963): *Medical Annual*, 81st ed., p. 446. Bristol: John Wright.
46. Lerner, A. B. and McGuire, J. S. (1964): New Engl. J. Med., **270**, 539.
47. McGuiness, B. W. (1961): Brit. Med. J., **2**, 563.
48. Mason, A. S. and Greenbaum, D. (1962): *Ibid.*, **2**, 445.
49. Hamilton, J. B. and Hubert, G. (1938): Science, **88**, 481.
50. Kirkeby, K., Hangaard, G. and Lingjaerde, P. (1963): Acta med. scand., **174**, 257.
51. Wurtusan, R. J., Axelrod, J. and Phillips, L. S. (1963): Science, **142**, 1071.
52. Conway, H. and Starke, R. (1951): Plast. Reconstr. Surg., **8**, 354.
53. Belisario, J. C. (1957): Acta derm.-venereol. (Stockh.), **37**, 165.
54. Castor, C. W. and Burton, L. B. (1950): Endocrinology, **47**, 234.
55. De Kleine, E. H. (1952): Plast. Reconstr. Surg., **9**, 473.
56. Conway, H., Gillette, R., Smith, J. W. and Findley, A. (1960): *Ibid.*, **25**, 117.
57. Murray, R. D. (1963): *Ibid.*, **31**, 275.
58. McGugan, A. D., Shuster, S. and Bottoms, E. (1963): J. Invest. Derm., **40**, 271