Pharmacologic Control of Surface Scarring in Human Beings

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A hypothetical basis for control of surface scar in human beings is: lathyrism produces poorly cross-linked collagen in healing wounds; poorly cross-linked collagen is more susceptible to digestion by tissue collagenase than is normally cross-linked collagen; and colchicine stimulates tissue collagenase activity. Therefore, treatment of patients with abnormal deposits of surface scar by excising the scar, inducing lathyrism, and administering colchicine should tend to correct abnormal balance between collagen synthesis and collagenolysis and result in a small scar with improved physical properties. Ten patients with massive keloids, resistant to conventional therapy by excision, grafting, and/or intralesional injection of steroids, have been treated by excising the keloid, grafting the defect, inducing lathyrism with Beta aminopropionitrile fumurate or penicillamine and administering colchicine. Patients were followed for 18 months to five years. No toxicity or untoward side effects from therapy were observed. No patients developed recurrent keloids while undergoing treatment. All patients showed some change in the amount of scar which persisted during the period of study. This data supports the hypothesis that lathyrism and colchicine therapy exert a measurable beneficial effect on surface scar in human beings.

PRESENT DATA suggest that excessive scarring due to abnormal deposition of collagen in healing skin wounds is the result of an abnormal equilibrium between net collagen synthesis and deposition and collagenolysis at neutral pH.[4,5] Although it is not known whether keloids are the result of increased (or prolonged) collagen synthesis or decreased (or shortened) tissue collagenase activity, the end result is the same.[9]

Because the degree of cross-linking affects susceptibility of collagen to collagenase degradation, a theoretical potential exists for controlling the amount of collagen in a healing wound by reducing cross-linking.[8] Cross-linking of newly-synthesized collagen can be reduced by inducing lathyrism—a condition caused by inhibiting lysyl oxidase activity. Beta aminopropionitrile and penicillamine are powerful lysyl oxidase inhibitors. Thus, it is theoretically possible to alter dynamics of collagen deposition and collagen removal by inhibiting cross-linking with BAPN and penicillamine.

Tissue collagenase kinetics can be accelerated in hu-

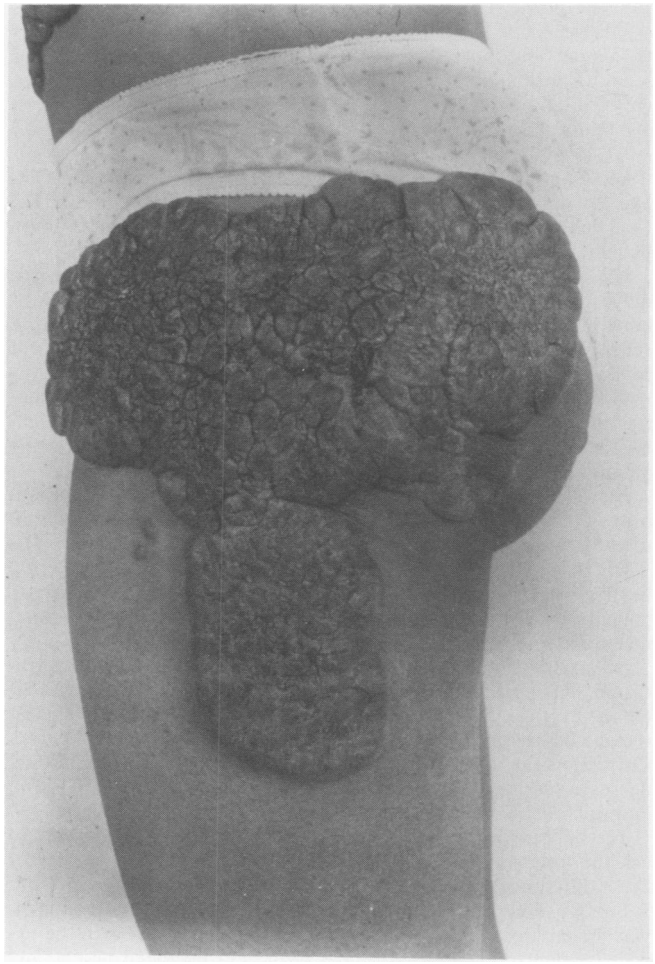

FIG. 1. Donor site on 16 year old female with abdominal keloid. Chronic infection produced drainage and odor.

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man rheumatoid synovial tissue under tissue culture conditions (and in some normal tissues in animals) by administering colchicine.[3,7] It is possible, therefore, that the lytic or destructive side of the scar metabolism equation also can be manipulated pharmacologically. To test the hypotheses that excessive scar tissue in human beings might be reduced significantly by reducing cross-linking of collagen while simultaneously accelerating tissue collagenase kinetics has been tested in ten patients with massive keloids resistant to injection, excision, and grafting.

Materials and Methods

All patients had recurrent keloids as defined by excessive scar tissue which did not follow the outline of the original wound, and formed a pedunculated shape larger on the surface than at the base. All patients had been treated previously by excision and closure or excision and grafting. Six patients received intralesional triamcinolone acetonide solution without discernible effect. One patient was an 8-year-old child, and one patient was a 17-year-old youth. The remaining patients ranged in age from 21 to 65 years. Eight patients were black; two patients were white. Eight patients were male; two were female. All of the patients were in good health except for recurrent keloids. After appropriate physical examination and laboratory tests to rule out unsuspected or undiagnosed chronic disease, patients were admitted to the hospital for elective excision of all or some of their keloids. Excision was performed to a depth of normal subcutaneous tissue. A rim of keloid was not retained. Horizontal plane dissection extended to, but not into, normal skin. An intermediate thickness (0.014–0.016 inch) split-thickness skin graft was applied to the wound immediately. Silk sutures tied over a Dacron® stent were used to maintain the graft in proper position for five days. Following removal of sutures, grafts were protected with Xeroform® gauze dressing for ten days. Donor sites were dressed with Xeroform gauze and allowed to epi-

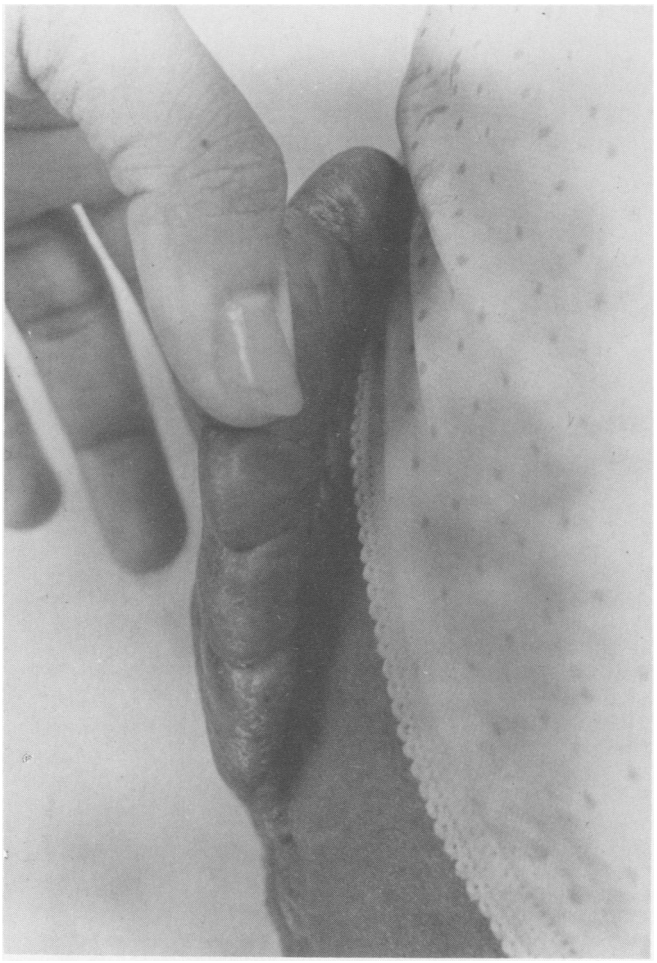

FIG. 2. Lateral view of keloid shown in Figure 1. Pedunculated shape is different from hypertrophic scar which follows outline of wound.

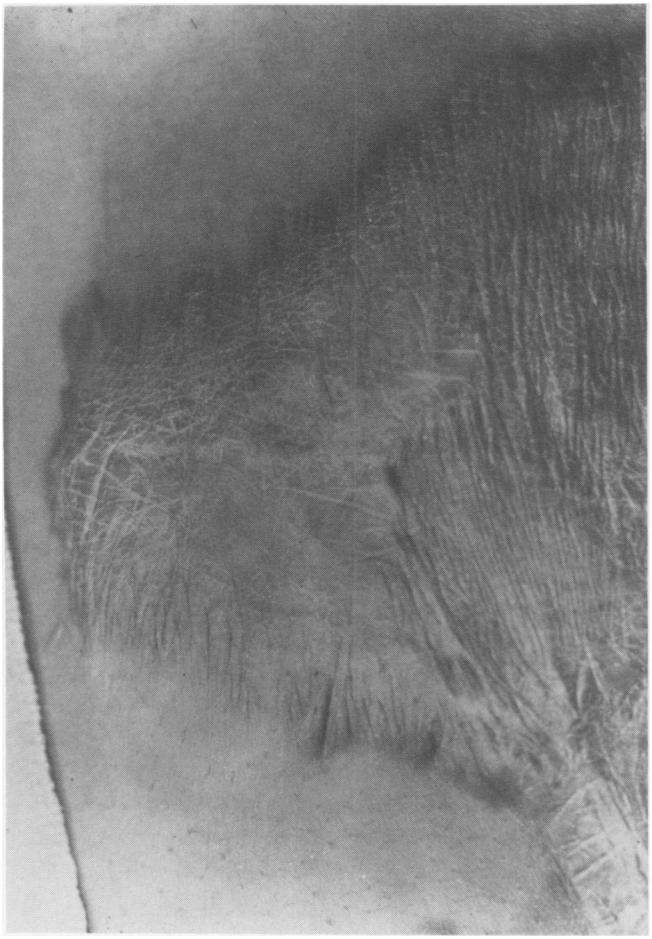

FIG. 3. Donor site shown in Figure 1 and 2 six months following excision, grafting, and administration of BAPN and colchicine.

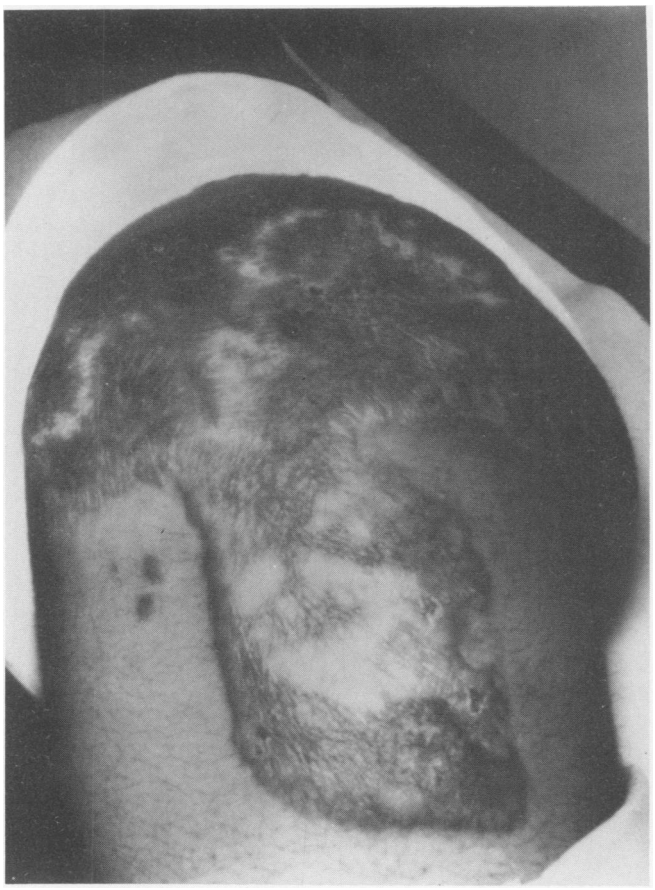

FIG. 4. Donor site shown in Figure 3 five years following treatment. A large keloid has been converted into a moderate size hypertrophic scar. No ulceration, drainage, or infection.

thelialize beneath the dressing until the gauze separated without hemorrhage.

As soon as epithelization of the donor area was complete (10–12 days for most patients), colchicine (one tablet by mouth three times a day) was administered. At the same time the keloid first started to appear following previous surgery, controlled lathyrism was induced with beta aminopropionitrile fumarate (BAPN). BAPN was used in nine adult patients; penicillamine was administered to the 8-year-old child. One gram per day of BAPN fumarate in four divided doses of 250 milligrams each was administered by mouth for 21 days. Penicillamine was administered in increasingly larger doses to a point of tolerance as conventionally utilized in patients with Wilson's disease. The administration of BAPN was limited to 21 days. Penicillamine was administered for three months; colchicine was administered for four months. The patients have had periodic follow-up examinations for between 18 months and five years. All patients have been followed for at least twice as long as the development of their keloids following previous surgery.

Results

No patients exhibited toxicity, hypersensitivity, or other untoward signs, symptoms, or laboratory abnormalities. No patient developed a keloid or hypertrophic scar while under treatment or for three months thereafter. Within two years of treatment all patients developed some degree of hypertrophic scarring, but no patient developed a recurrent keloid with similar proportions to the preoperative condition. (Figs. 6–10) Five patients developed a hypertrophic scar in the donor site; five patients healed their donor sites without abnormal scar tissue.

Discussion

All patients were improved by a combination of excision and grafting of keloids and postoperative administration of a lathyrogenic agent and colchicine. Appropriate controls to test the effect of surgery, surgery and colchicine, or surgery and lathyrism could not be performed in these patients. Because all patients had

FIG. 5. Donor sites two years following BAPN therapy.

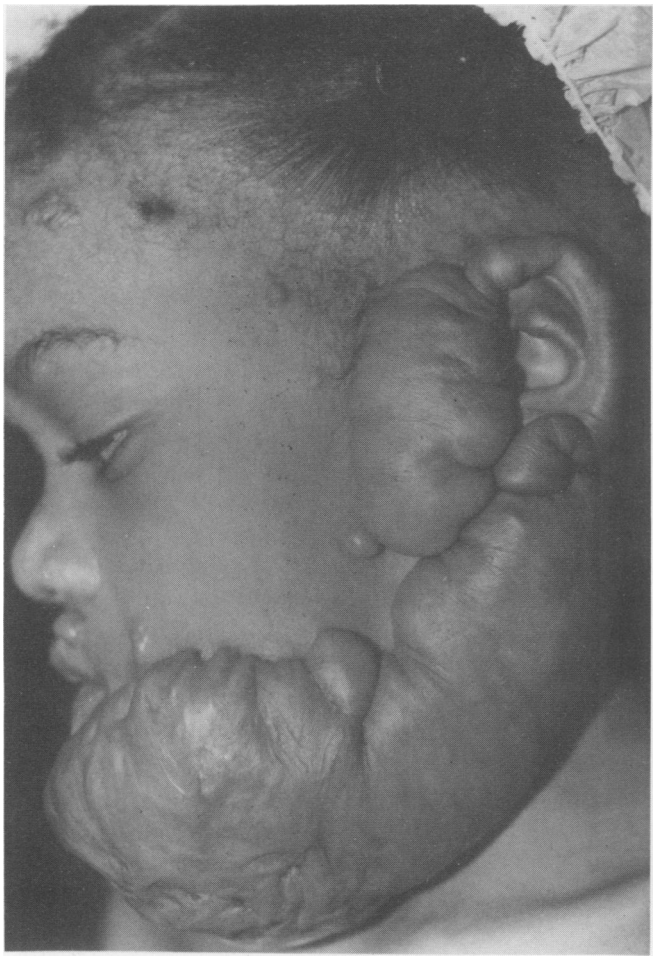

FIG. 6. Massive recurrent keloid following therapy for burns.

been operated upon at least once previously without the use of pharmacologic agents, an imperfect control for surgery alone was part of the study. Because the tendency to form keloids changes with time, however, surgery at different times in the same patient cannot be considered an adequate control. One patient (M.G.) (Figs. 1–5) provided an exception to this criticism. Patient M.G. had severe keloids over such an extensive area that surgery was staged over a 14-month interval. Between stages an inflammatory condition which required surgical drainage developed in a new area. During healing of the drainage site, anticollagen agents were not administered. A severe keloid developed in the drainage site. During subsequent surgery and treatment with BAPN and colchicine, keloids did not develop. Thus, the time factor in development of a keloid was controlled serendipitously in one patient.

The results of this study do not suggest that BAPN, penicillamine, and colchicine necessarily are the agents of choice to control keloids in human beings. The results do suggest, however, that use of the principle of induced lathyrism and accelerated collagenolysis can

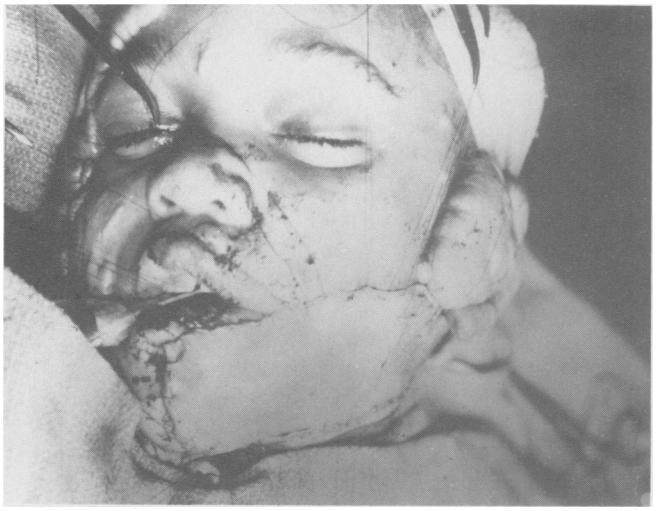

FIG. 7. Excision and grafting of inferior portion of keloid shown in Figure 6.

shift an abnormal equilibrium between collagen deposition and collagenolysis to a more normal range, and that severe keloid formation can be converted to moder-

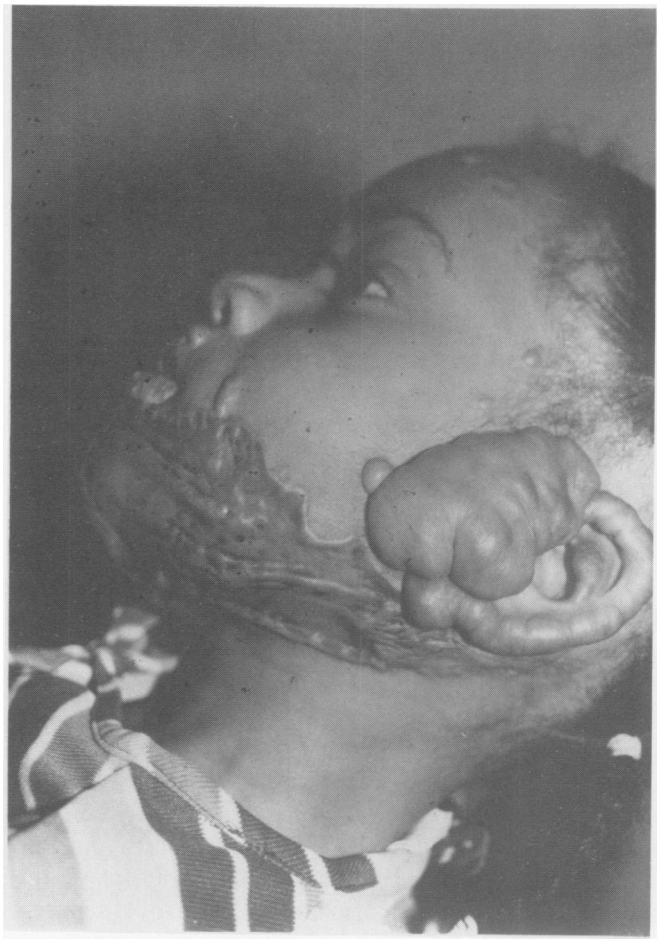

FIG. 8. Appearance of graft and superior keloid in patient shown in Figure 7 one year following treatment with penicillamine and colchicine.

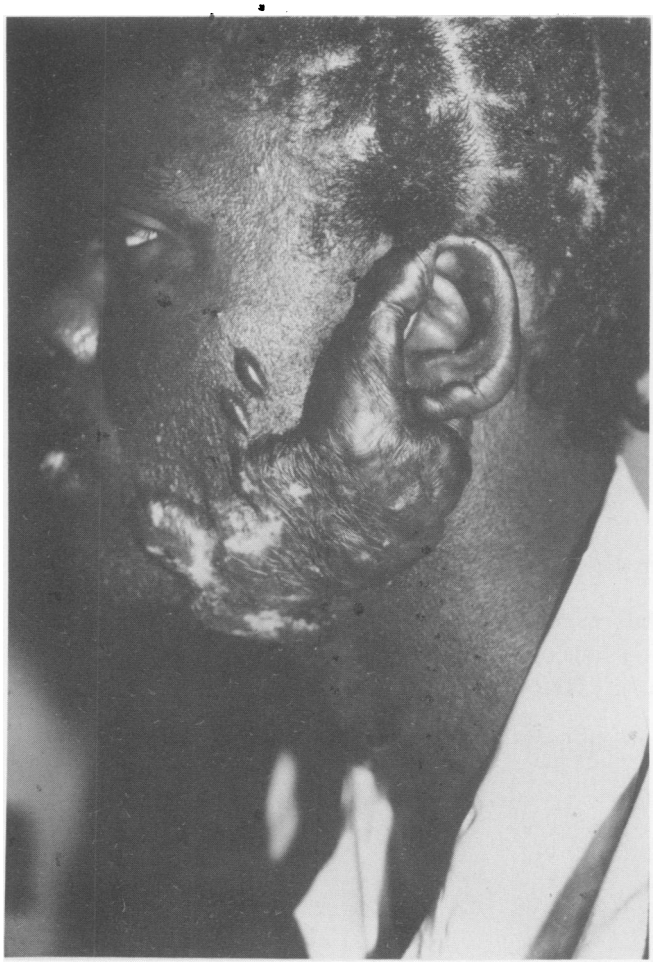

FIG. 9. Recurrent keloid of face following surgical treatment of 3° burns and scars.

ately severe hypertrophic scarring. The theoretical possibility of restoring normal equilibrium to collagen synthesis and degradation in a surgical wound is supported by the results in ten patients. It is important to note that the dose of the agent and the time of administration were selected arbitrarily. As far as is known, colchicine can be administered indefinitely, but lathyrogenic agents, particularly BAPN, have a finite period of safe administration. Previous work in animals suggests that the healing wound can be affected selectively by a relatively miniscule dose of a powerful lathyrogen.[1] Thus, it may be possible to administer powerful lathyrogenic agents with good results in larger or smaller doses than were used in this study. Other lathyrogenic agents such as penicillamine may be used for longer periods of time.

Cross-linking of collagen and collagenolysis are not the only points where pharmacologic control of scar tissue in human beings may be possible in this decade. Although previous studies on the use of proline analogues were disappointing at a phase II level (animal toxicity studies), recent studies indicate 3.4 dehydroproline, at least, may be safe in small doses in human beings.[2,10] Clinical control of scar tissue in human beings may require multiple agents used in subtoxic doses to produce clinically significant effects on connective tissue synthesis and deposition. A similar approach, of course, has been effective in the treatment of cancer. Such an approach for the control of scar tissue might involve the use of an agent such as dehydroproline to reduce synthesis of new collagen; reduced amounts of new collagen synthesized under dehydroproline administration could then have some cross-linking inhibited by the use of a lathyrogenic agent such as BAPN. Cross-links which formed under BAPN administration might be chelated by a third agent such as penicillamine. Finally, reduced amounts of collagen synthesized under the effect of dehydroproline, poorly cross-linked under the effect of BAPN, and chelated by penicillamine might be abnormally sensitive to accelerated tissue collagenase stimulated by colchicine. Dehydroproline, BAPN, penicillamine, and colchicine act at dif-

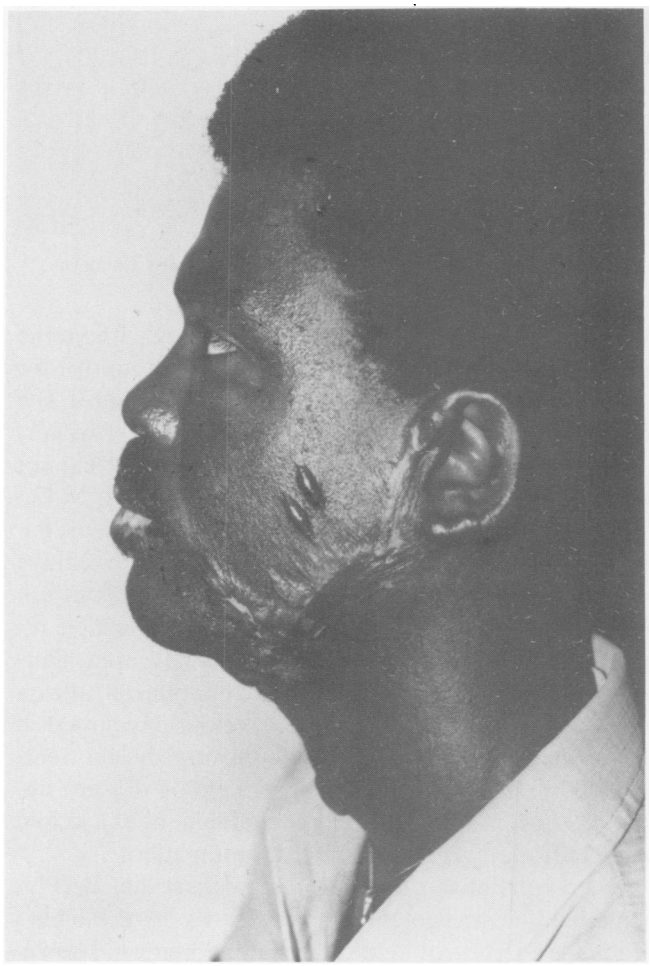

FIG. 10. Patient shown in Figure 9 two and a half years following excision, grafting, and treatment with BAPN and colchicine.

ferent sites in the synthesis, deposition, and removal of dense connective tissue. The effects of penicillamine and BAPN have been found to be additive.[6] Experiments are needed now to test the hypothesis that other available agents also are additive and can be used in conjunction with each other. Such experiments can be performed in laboratory animals.

In the final analysis, phase III or human testing will be needed to determine whether pharmacologic adjuvants make a significant difference in keloid and hypertrophic scar formation. Such studies are difficult to perform. Human testing of new agents requires patient safeguards that make adequate controls difficult. Although the present group of patients does not provide adequate controls for all the questions which need to be answered, it seems that the general principle of controlled lathyrism and tissue collagenase stimulation does make a clinically significant difference and should be tested in larger populations of human beings.

Summary and Conclusion

Ten patients with recurrent keloid following conventional therapy were treated with excision and grafting followed by administration of a lathyrogenic agent and colchicine. No toxic or untoward signs, symptoms, or laboratory determinations were encountered. All patients were improved during an 18-month to three-year follow-up period. Improvement can be described best as conversion of massive pedunculated keloid to moderate size hypertrophic scar. Adequate controls for each patient were not possible in this study.

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