Synthetic retinoids in dermatology

Elizabeth H. Heller, MD
Norman J. Shiffman, MD, FRCPC

The potential of vitamin A, or retinol, in the treatment of a variety of skin diseases has long been recognized, but because of serious toxic effects this substance generally could not be used. The recent development and marketing of two relatively nontoxic synthetic analogues, which are known as retinoids, has made it possible to treat some of the diseases that are resistant to standard forms of therapy. Isotretinoin is very effective in cystic and conglobate acne, while etretinate is especially useful in the more severe forms of psoriasis. Good results have also been obtained in other disorders of keratinization. Vitamin A and its derivatives apparently have an antineoplastic effect as well and may come to be used in both the prevention and the treatment of epithelial cancer. In many of these diseases the retinoids act by enhancing the normal differentiation and proliferation of epidermal tissues, but the exact mechanisms are not well understood. Their influence on the intracellular polyamines that control the synthesis of nucleic acids and proteins may be an important factor. Although the retinoids have few serious systemic effects, they are teratogenic, and because they persist in the body their use in women of childbearing potential is limited.

Si on connaît depuis longtemps ce que peut donner la vitamine A (ou rétinol) dans le traitement de certaines dermatoses, son emploi est généralement interdit par des effets toxiques graves. Récemment, la synthèse et la mise en marché de deux analogues relativement peu toxiques, les rétinoïdes, ont permis de traiter des dermatoses résistantes aux traitements habituels. Il s'agit de l'isotrétinoïne, très efficace contre l'acné kystique et pustuleuse, et de l'étrétinate, fort utile dans les formes graves du psoriasis. On obtient des résultats intéressants dans certains autres troubles de la kératinisation. La vitamine A et ses dérivés semblent posséder aussi une action antinéoplasique qui servira peut-être un jour à prévenir et à traiter les épithéliomas. Dans beaucoup de ces maladies, les rétinoïdes agissent en favorisant, par des voies encore mal comprises, la différenciation et la prolifération normale des tissus épithéliaux. Leur action sur les polyamines intracellulaires qui régissent la synthèse des acides nucléiques et des protéines serait un facteur important. Les rétinoïdes ont peu d'effets généraux graves, sauf qu'ils sont tératogènes; comme ils persistent dans l'organisme, il faut s'en garder chez les femmes susceptibles d'être mères.

Vitamin A, or retinol, is a fat-soluble vitamin important in reproduction, the visual cycle, and the differentiation and maintenance of epithelial tissues. An esterified form, vitamin A palmitate, is supplied in the diet by animal sources, such as fish-liver oil, eggs, butter and animal liver, and by fortified margarine. Vitamin A is also derived from the carotenoid pigments, particularly β-carotene, which is found in many green and yellow vegetables. The structures of β-carotene, retinol and retinol's important metabolic derivatives, retinal and retinoic acid (tretinoin), are shown in Fig. 1.

Once in the lumen of the gut vitamin A palmitate is hydrolyzed by pancreatic lipase to retinol, which is then absorbed into the gastrointestinal mucosa. Beta-carotene is hydrolyzed in two steps to retinol. Theoretically, one molecule of β-carotene can produce two molecules of retinol, but in humans the conversion is inefficient, and four times as much carotene as retinol is needed to maintain the eyes' normal capacity for adaptation to the dark.[1]

In the mucosal cells of the gastrointestinal tract retinol is esterified to form retinyl esters, which are then transported to the liver for storage via chylomicrons in the blood and lymphatic channels. Retinol is released from the liver in association with retinol-binding protein and circulates as a protein–protein aggregate with prealbumin; the aggregate, in turn, binds one molecule of thyroxine.

In the peripheral tissues retinol undergoes reversible oxidation to retinal and then irreversible oxidation to retinoic acid. Although the mechanisms are poorly understood, it appears that retinol, retinal and retinoic acid all contribute in specific ways to the biologic functions attributed to vitamin A.

The only system in which the action of vitamin A is understood at a molecular level is the visual cycle. Retinol is metabolized to all-*trans*-retinal and then to the isomer 11-*cis*-retinal, which interacts with opsin to form the visual pigment rhodopsin.[1] Hence, retinal is the form of vitamin A important in the visual cycle, and one of the effects of vitamin A deficiency is night blindness.[2]

Although little is known about the role of vitamin A in the reproductive tract, animals deprived of retinol are unable to maintain and deliver a

From the Division of Dermatology, the Wellesley Hospital, Toronto

Correspondence to: Dr. Elizabeth H. Heller, 345 Victoria St., London, Ont. N6A 2C7

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viable fetus, and testicular atrophy due to loss of spermatids is observed.[3] Supplementation with retinol, but not retinoic acid, reverses these abnormalities.

Finally, vitamin A is important in the growth and normal differentiation of epithelial tissues. Experimentally, vitamin A deficiency causes metaplasia of glandular, ciliated, mucus-secreting epithelium and hyperkeratosis of keratinizing epithelium.[4,5] In the human skin these changes produce a condition known as phrynoderma, in which there are many minute follicular papules. Retinoic acid, inactive in the visual and reproductive systems, can correct the abnormalities seen in the epithelial tissues of vitamin-A-deficient animals.[6]

The development of retinoids

Because of the similarity between phrynoderma and many other skin diseases involving abnormal keratinization, it was at first thought that a deficiency of vitamin A might be involved in the pathogenesis of the other diseases. Vitamin A was therefore used orally in an attempt to treat diseases such as ichthyosis, Darier's disease (keratosis follicularis), psoriasis and even acne.[7,8] The high dosages required, however, were associated with serious toxic effects (increased intracranial pressure, with headache and irritability, as well as changes in the skin, mucous membranes and skeleton). Retinoic acid has been administered topically, mainly in the treatment of acne, but causes skin irritation; it is also impractical for conditions such as Darier's disease in which continuous treatment of large areas of the body is required. The toxic effects of orally administered retinoic acid on the central nervous system are similar to those of vitamin A.[9]

A search for less toxic substitutes for vitamin A led to the development of the safer analogues known as retinoids. Retinoids are formed by modification of the vitamin A molecule at any one of its three main components: the cyclic end group, the polar end group and the polyene side chain (Fig. 2). The first retinoid to be synthesized, in 1955, was 13-*cis*-retinoic acid, also known as isotretinoin (Ro 4-3780). It was first used to treat psoriasis in Europe in 1973, has been used in trials in the United States since 1976 and is approved for treatment of severe nodulocystic acne that has not responded to standard therapy. Since 1982 it has been marketed by Hoffmann-La Roche under the trade name Accutane. The aromatic retinoid etretinate (Ro 10-9359) was synthesized in 1972 and has also been the subject of much study. It was recently released as Tegison by the same manufacturer.

Besides being important in the treatment of disorders of keratinization, including acne, the retinoids are of great interest to oncologists because of the possibility that they can be used to prevent and treat a variety of premalignant conditions. We will now review the mechanisms of action, pharmacokinetics, side effects and clinical applications of these two drugs in dermatology.

Mechanisms of action

The effects of vitamin A and retinoids on the skin are poorly understood, but many possibilities have been proposed on the basis of experimental observations.

The cell growth and proliferation that figure in many skin diseases depend in part on the intracellular polyamines that control the synthesis of nucleic acids and proteins.[10] In both psoriasis[11] and the early stages of cancer[12] the activity of ornithine decarboxylase, the rate-limiting enzyme in polyamine biosynthesis, is increased. In psoriasis etretinate therapy causes the levels of this enzyme to fall;[13] the retinoids also block the induction of ornithine decarboxylase by tumour promoters.[14]

In the cell, proteins that bind retinol and retinoic acid carry these substances to the nucleus, where they have an effect on RNA synthesis that is analogous to that of the steroid hormones.[15,16] This effect may help explain how retinoids can induce and maintain terminal differentiation in malignant cell lines.[17]

Gap junctions are lost during malignant transformation; retinoids stimulate their production and the synthesis of glycoproteins, both of which are important in cell communication, adhesion and growth.[18,19]

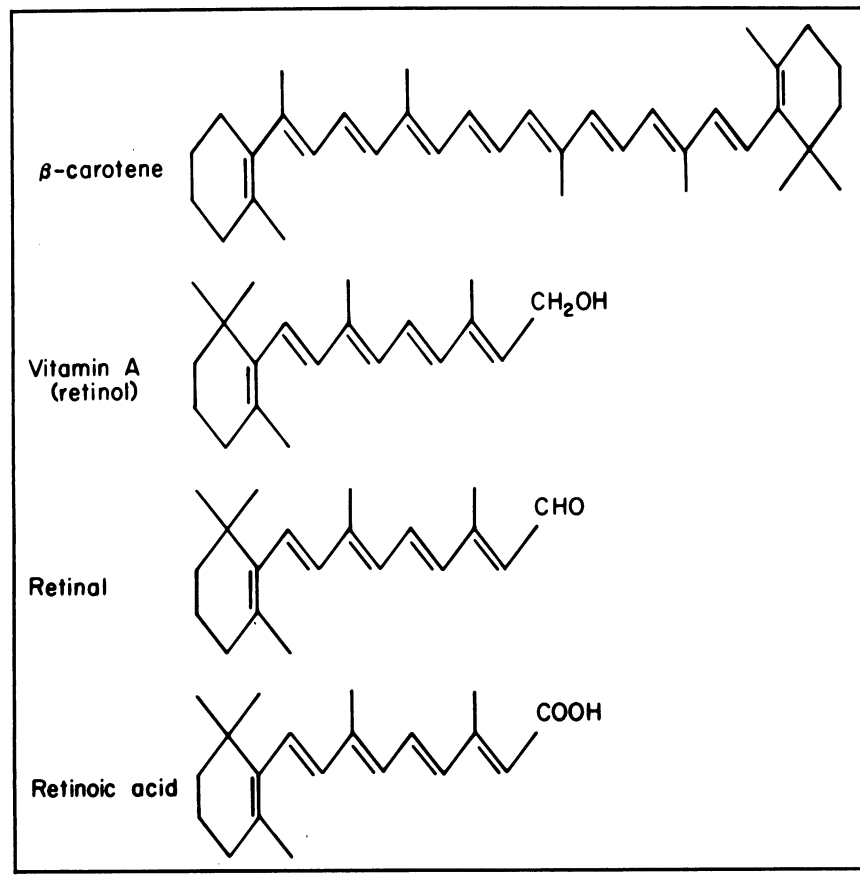

Fig. 1—Structures of vitamin A and related compounds.

Physiologic doses of retinoids also stimulate killer T-cell production and cell-mediated cytotoxicity, which may well be important in the treatment of cancer.[20]

Retinoids thus act by enhancing the normal differentiation and proliferation of epidermal tissues. Although their mode of action is not fully known, control of polyamine synthesis by inhibition of the rate-limiting enzyme appears to be an important factor.

Pharmacokinetics

Isotretinoin is rapidly absorbed after oral administration, with peak levels being reached in 2 to 3 hours. Virtually all of the drug is bound to albumin and is metabolized to 4-oxo-isotretinoin. The elimination half-lives with either single or multiple dosing are 10 to 20 hours and 24 to 29 hours for the drug and its metabolite respectively.

Etretinate is rapidly hydrolyzed in the gut, liver and blood to Ro 10-1670; plasma concentrations of this metabolite far exceed those of etretinate. Both etretinate and Ro 10-1670 are highly bound to plasma proteins. The half-life of each after a single oral dose is only 6 to 13 hours, but the prolonged elimination after multiple dosing suggests that there is a deep tissue compartment, perhaps adipose tissue, where etretinate was recently shown to accumulate.[21] In fact, the half-life is 80 to 100 days in patients receiving long-term therapy, and the drug is detectable in the blood 3 months after the end of treatment.[22] Considering the teratogenicity of this class of drugs, this persistence has important therapeutic implications.

Toxic and side effects

Excessive vitamin A intake can result in either acute or chronic toxic effects. The most prominent features of chronic hypervitaminosis A are dry scaling skin, cheilitis and loss of hair, followed by bone pain, anorexia, and headache and diplopia due to increased intracranial pressure. Hepatosplenomegaly often occurs, with perisinusoidal deposition of lipids and fibrosis seen in biopsy specimens.[23] Swelling of the feet is common in children and often causes refusal to walk; cortical hyperostosis may be seen on x-ray films.

In contrast to vitamin A, the relatively nontoxic retinoids have few serious systemic side effects. Of major importance, however, is their teratogenicity. The retinoids are not mutagenic, but they do cause serious fetal malformations, including major abnormalities of the central nervous system, and cardiac and ear defects.[24] It is imperative that physicians be certain that their patients are not pregnant before starting treatment with isotretinoin and that the patients use reliable methods of birth control before and during therapy and for a full month after therapy is stopped. Because of its long half-life etretinate is generally not recommended for women of childbearing potential. In spite of warnings, however, 13 pregnancies in Canadian women who were using isotretinoin have been reported to the drug's manufacturer.[25] One spontaneous and eight induced abortions resulted.

The mucocutaneous side effects of retinoids are dose-related, tolerable and reversible. Most are really extensions of the drugs' actions. Retinoids impair barrier function and enhance evaporation, the results being dryness of the skin and mucous membranes, thirst and increased percutaneous absorption of other topically applied compounds. Dryness of the lips occurs in almost all patients, which makes double-blind studies virtually impossible. There can be severe cheilitis and also epistaxis from dryness of the nasal mucosa. Patients may experience generalized pruritus. All these changes are managed with topical lubricants, and by avoiding exposure to sunlight a patient with facial dermatitis may find improvement.

Paronychia, changes in hair texture and increased skin fragility can also occur with retinoid therapy. A more troublesome but uncommon side effect is a dose-dependent, reversible diffuse thinning of the hair that first appears 3 to 8 weeks after the start of therapy,[26] especially with etretinate.[27]

Blepharoconjunctivitis occurs in

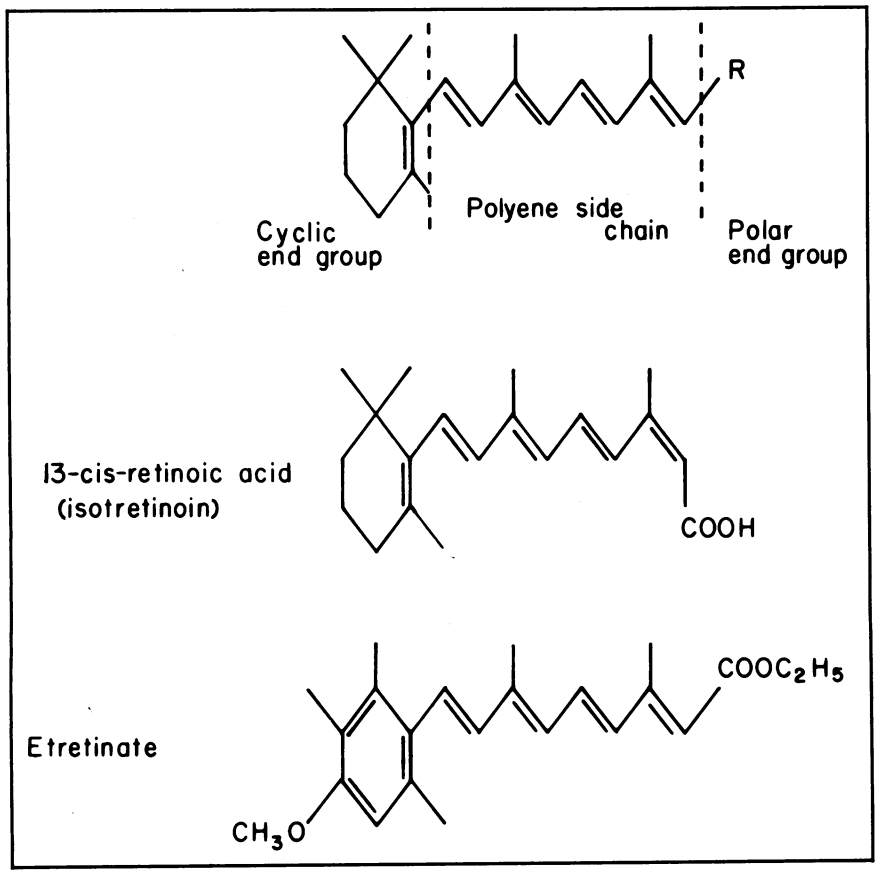

Fig. 2—Modifications of vitamin A structure yielding two synthetic retinoids now used as drugs.

up to half the patients treated with isotretinoin but responds to topical antibiotic therapy.[27] Culture of conjunctival swabs shows *Staphylococcus aureus* in a high proportion of patients treated with isotretinoin; this may represent secondary colonization of a dry, susceptible cornea. Isotretinoin inhibits lipid production in the skin and may have a similar effect on the meibomian glands.[28] Some patients have only a subjective feeling of dryness of the eyes, but this may be so troublesome that they cannot tolerate their contact lenses.

A recently reported but probably not uncommon side effect is the development of excessive granulation tissue at the site of healing cystic acne and adjacent to nail plates in patients treated with isotretinoin and etretinate respectively.[29,30] This phenomenon seems unrelated to dosage and is reversible by discontinuation of treatment. It is best managed with topical applications of trichloroacetic acid or silver nitrate or with surgical excision.

In addition to these side effects, acne may temporarily become worse in the first few weeks of treatment, and the oral administration of corticosteroids during this period may be indicated.

Of the two compounds, etretinate seems to cause more palmoplantar desquamation, thinning of the hair and pruritus, and isotretinoin more conjunctivitis, facial scaling and cheilitis.[27] Dryness of the skin and mucous membranes is so strongly associated with both drugs that its absence raises the question of patient compliance.

Effects on lipid metabolism

A mild, dose-dependent increase in the serum triglyceride level, usually to between 2.25 and 4.50 mmol/L, occurs commonly with isotretinoin therapy and less frequently with etretinate therapy.[27,31] It is rarely of clinical significance. Over the first 4 weeks of treatment the concentrations of low- and very-low-density lipoproteins and cholesterol increase and the level of high-density lipoprotein decreases. The levels then stabilize, but after treatment is stopped they return to normal within 8 weeks.[32] Hence, the current recommendation is to check the lipid levels at the start of treatment and 2 to 3 and 4 to 6 weeks thereafter.[31] Only if the triglyceride concentration exceeds 4.50 mmol/L at 4 to 6 weeks is it necessary to continue monitoring the lipid levels. Therapy should be stopped if the triglyceride level exceeds 8.0 mmol/L, because there is a risk of pancreatitis.

More dramatic increases in the triglyceride level have been seen in patients who were obese, consumed excessive amounts of alcohol or had a family history of hyperlipidemia or other risk factors.[33,34] Eruptive xanthomas[33] and pancreatitis[31] may occur. Patients at risk should be put on a low-fat diet and have their alcohol intake limited in an attempt to prevent the triglyceride level from increasing.[31] The significance of an elevated triglyceride level and short-term increases in the cholesterol concentration in terms of heart disease is unknown,[32] but no cardiac complications have been reported.

Hepatic effects

Unlike retinol, the retinoids are not stored in the liver, but they are metabolized there, so the liver is a potential site of toxic effects. The mildly abnormal results of liver function tests sometimes seen are often corrected while treatment continues and are reversible once it is stopped.[28] Although liver biopsy has shown deterioration in patients predisposed to liver damage and receiving etretinate, the changes were not consistent and were not seen if the pretreatment biopsy had shown normal histologic features.[35] Kanigsberg and DesGroseilliers[36] reported a case in which a full course of isotretinoin therapy was given despite a mild but persistent elevation of the patient's hepatic enzyme levels during treatment; the results of a subsequent liver biopsy were normal. Serious hepatotoxic effects, such as are seen with vitamin A, have not been reported with the retinoids.

Musculoskeletal effects

Arthralgias and myalgias occur in up to 16% of patients receiving isotretinoin for acne and are usually easily managed with analgesics or nonsteroidal anti-inflammatory drugs.[31] However, a more serious side effect is the development of skeletal hyperostosis, in which new bone forms in areas of ligamentous attachment. This occurs in long-term high-dose treatment with isotretinoin. The first report was of four patients with ichthyosis who were treated with more than 2 mg/kg daily for at least 2 years.[37]

It is currently recommended that skeletal radiologic surveys be carried out at the start and after 6 and 12 months of treatment in patients given high doses of isotretinoin. To date, skeletal abnormalities have not been reported with etretinate therapy or in acne patients treated with isotretinoin.

Effects on the central nervous system

In the central nervous system the side effects of retinoids are rare and range from mild headache to visual changes and papilledema. The syndrome of pseudotumour cerebri has been reported in a small number of patients receiving isotretinoin;[31] some of them were also taking either tetracycline or minocycline. It is not known whether this represents a drug interaction, but it would seem prudent to avoid using these antibiotics concurrently with isotretinoin.

Other toxic effects

A recent update on the side effects of isotretinoin reported the occurrence of hyperuricemia (twice in association with symptomatic gout), regional ileitis and, in patients with cystic acne, corneal opacities.[38] Other abnormalities that seem to have had no clinical significance include increases in the peripheral blood platelet count and total protein level and in the urine specific gravity and leukocyte count.[31]

Clinical applications

Psoriasis

The common type of psoriasis, psoriasis vulgaris, is characterized by erythematous plaques with a silvery scale. This chronic disease may evolve to a more severe form in which an erythematous, scaling

eruption covers almost the entire body. In addition, there are various pustular forms of psoriasis, which may be either localized or acute and generalized, with high fever, systemic toxic effects and a poor prognosis.

Erythrodermic psoriasis, generalized pustular psoriasis and pustular psoriasis of the palms and soles, all of which have been difficult to treat, respond particularly well to etretinate therapy.[39-41] Psoriasis vulgaris, however, responds less well, and although etretinate therapy is about as effective as treatment with anthralin, the Goeckerman regimen (the use of tar ointments plus ultraviolet radiation of short wavelength [UVB; 290 to 320 nm]) or photochemotherapy (the use of a psoralen plus ultraviolet radiation of long wavelength [UVA; 320 to 400 nm], also known, therefore, as PUVA therapy) it is unlikely to replace these standard forms of treatment, because they have fewer side effects.[42]

The response to etretinate is dose-dependent,[43] and the best results are seen with daily rather than alternate-day or alternate-week treatment.[44] However, this retinoid does not seem to alter the natural history of the disease, and relapses may occur while maintenance treatment continues, as well as when it ends.

The combination of etretinate with other forms of treatment has met with more success. For example, when etretinate and PUVA therapy were combined, the number of irradiation sessions required was reduced by 40%, and the cumulative dose of UVA radiation, the factor most related to carcinogenesis, was reduced by two thirds.[45] Etretinate has similar advantages when used with UVB radiation.[46]

The combination of etretinate and anthralin has given better results than either agent alone,[47] and the combination of etretinate in low daily doses (0.50 to 0.66 mg/kg) and corticosteroids administered topically has given good results with few side effects,[48] thus proving to be a good form of treatment for outpatients with mild to moderate psoriasis. Adding etretinate therapy to PUVA, UVB or anthralin treatment is often effective in patients who have become resistant to a single form of therapy.

Other disorders of keratinization

Several other disorders of keratinization, previously almost untreatable, have responded well to treatment with retinoids, particularly etretinate.

The ichthyoses, a group of disorders characterized by fish-like scaling and hyperkeratosis, with or without erythema, can be treated with either retinoid.[49,50] The results have been especially good in lamellar ichthyosis and epidermolytic hyperkeratosis. Although few patients have had complete clearing of these disorders, their tolerance of heat and ability to sweat has increased, and they have had a much improved appearance.

In Darier's disease, an autosomal dominant condition characterized by a defect in the tonofilament–desmosome complex that connects epithelial cells in the epidermis, firm, greasy papules develop in seborrheic areas. These can become generalized and complicated by a foul odour from secondary infection. Treatment was poor in the past because the vitamin A used was too toxic for the continuous treatment needed to prevent relapse. Isotretinoin[51] and etretinate,[52] however, have both been shown to be effective: in one study over 85% of 98 patients showed definite improvement in 5 to 8 weeks.[51]

Good results with retinoid therapy have been seen in pityriasis rubra pilaris,[53] porokeratosis,[54] subcorneal pustular dermatosis[55] and verrucous epidermal nevus.[56] The retinoids have also been used in the more severe forms of keratosis palmaris et plantaris,[57] which interfere with daily work or walking.

Lichen planus is generally fairly benign and often remits spontaneously. However, chronic lichen planus of the skin and mucous membranes can be severe, painful and difficult to treat. Etretinate therapy has been successful in over 75% of patients, with the best results occurring in the erosive–atrophic form of the disease.[58]

In the keratinizing disorders, retinoids seem to suppress but not correct the disease, and maintenance treatment with a reduced dosage is necessary. The probability of clinical improvement must be weighed against that of the potential long-term side effects for each patient.

Acne

Vitamin A has been used in the treatment of severe acne since the 1940s, when the similarity between acne comedones and the follicular hyperkeratosis of vitamin A deficiency was observed. Isotretinoin has now been shown to be very effective in severe cystic conglobate acne (Fig. 3). In 1979 Peck and coworkers[59] reported complete clearing in 13 of 14 patients treated with 2 mg/kg daily for 4 months; long-term follow-up showed that the remission persisted for up to 5 years.[60] Similar results were obtained in a double-blind crossover trial.[61] Since the release of isotretinoin for use in severe cystic acne 2 years ago, many studies and increasing clinical experience have testified to its effectiveness.[31,36]

A generally effective regimen with isotretinoin seems to be 1 mg/kg daily for 4 months, with a second course given if necessary after a wait of at least 2 months. Lower doses do not greatly reduce the incidence of side effects and result in higher rates of relapse.[31] Improvement can begin after 1 to 2 months of treatment but usually does not appear before 3 to 4 months. Peck and colleagues[61] found that the mean time to complete clearing after the end of treatment in 18 patients given a single course was 6 months. Isotretinoin works better and faster on the face than on the trunk, and lesions on the latter may require higher dosages.

Although a recent report has suggested using isotretinoin in cases of inflammatory noncystic acne with extensive scarring,[31] the drug is currently approved only for treatment of severe nodulocystic acne unresponsive to conventional therapy, which should include a full trial of systemic antibiotic therapy.

In acne, treatment with the effective retinoid, isotretinoin, decreases sebum production by 80% to 90% in 8 weeks.[62] There is a corresponding reduction in the size of the sebaceous glands.[63] After treatment ends, though, sebum production tend to return to normal even while clinical remission persists;[64] also, in

a few patients sebum production has been suppressed without there being a corresponding clinical response.[61,62] Therefore, other mechanisms, such as alteration of keratinization or inhibition of the growth of *Propionibacterium acnes*, are being considered. Isotretinoin's anti-inflammatory effects may be involved too.[65]

Isotretinoin is effective in related disorders and seems to be the treatment of choice in gram-negative folliculitis,[31,66] a complication of prolonged antibiotic treatment for acne. In this disorder the anterior nares become heavily colonized with gram-negative bacteria, which then cause severe inflammation of the skin and are difficult to eradicate. Isotretinoin is very effective in acne rosacea, which responds like acne vulgaris.[31,66] In the treatment of hidradenitis suppurativa the drug is a useful adjuvant, but it cannot cause resolution of the disease once undermining sinus tracts have formed; Shalita and associates[31] suggested a 4- to 5-month course of isotretinoin therapy in addition to treatment with antibiotics, intralesional application of steroids and surgical excision when necessary.

Cancer and the retinoids

The fascinating story of retinoids and cancer began in the 1920s, when a high incidence of gastric cancer appeared in rats fed a vitamin-A-deficient diet.[67] Further studies, in guinea pigs, showed that a diet deficient in vitamin A resulted in hyperkeratinization, squamous metaplasia and tumour formation in the epithelial tissues of the larynx, trachea, lungs, salivary glands, stomach and bladder.[68]

Experimentally, vitamin A has prevented chemically induced lung cancer,[69] and retinoic acid has caused dose-dependent regression of chemically induced skin papillomas.[70] A high intake of vitamin A in the diet has also been associated with a decreased incidence of lung cancer in humans.[71]

Over the past decade retinoids have been used in the prevention and treatment of various premalignant and malignant skin conditions in humans. In three patients with multiple basal-cell carcinomas[17] and another with multiple keratoacanthomas[72] isotretinoin had varied effects on existing tumours but prevented the development of new lesions until treatment was discontinued. Although the major role of retinoids seems to be preventive, etretinate has been used with some success in the treatment of actinic keratoses,[73] warts,[74] leukoplakia,[75] epidermodysplasia verruciformis[76] and cutaneous T-cell lymphoma (mycosis fungoides).[77] Isotretinoin has also been of benefit in patients with cutaneous T-cell lymphoma[78] and was found to induce differentiation of promyelocytes in a patient with acute promyelocytic leukemia.[79] Preliminary findings suggest that isotretinoin may be useful in adjuvant treatment of squamous epithelial malignant diseases.[80]

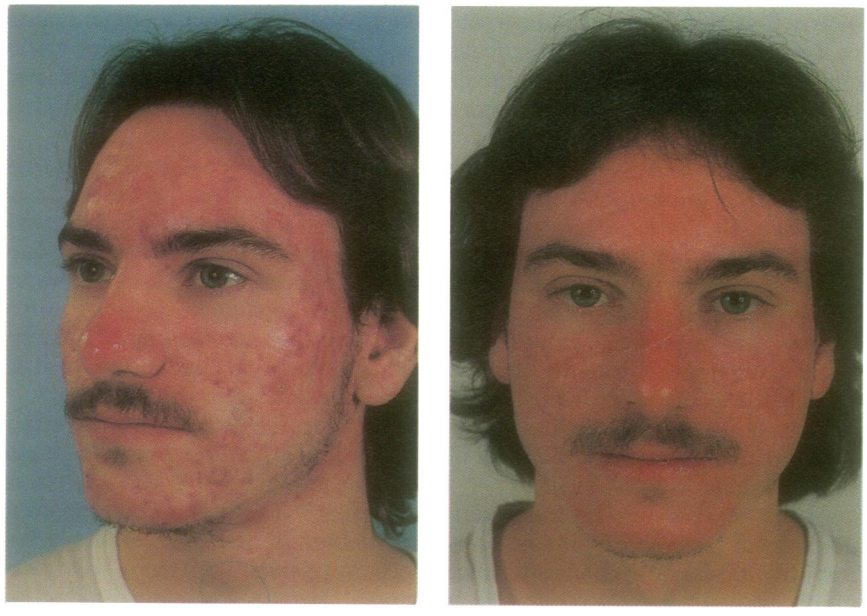

Fig. 3—Patient with severe acne before (left) and after 16 weeks of treatment with isotretinoin.

Conclusion

The retinoids are drugs of great potential in dermatology and oncology. They are definitely effective in severe acne, certain forms of psoriasis and other disorders of keratinization — all diseases for which there has been no satisfactory treatment. In psoriasis vulgaris etretinate is very useful in combination therapy, but further clinical trials and better knowledge of the long-term side effects will determine its exact role.

There is evidence that the retinoids are of value in the prevention and, to a lesser extent, the treatment of premalignant and malignant conditions of skin and epithelial tissue. In addition, retinoids with greater specificity for target organs and fewer systemic side effects are being developed by means of modification of the basic structures.[81] Whether a daily regimen could decrease the incidence of cancer in high-risk patients awaits the outcome of large clinical trials.

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