RETINOIDS AND RETINOID THERAPY - 1984

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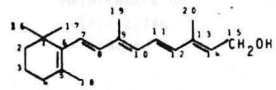
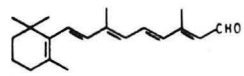
I. INTRODUCTION

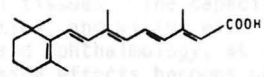
Contained within butter fat, fish oils, and egg yolk there exists a lipid soluble extract which was found early in the Twentieth Century to be essential for life. As the scientific understanding of vitamins progressed during the last eighty years, this material carried a succession of names, each representing a higher level of sophistication. They included "fat soluble A" (1), then vitamin A (2), and most recently retinol (3). Even before the discovery of vitamin A, however, investigators had identified and isolated from vegetable sources several naturally occurring carotenoid pigments, termed "carotenoids", the most familiar being beta-carotene, which is responsible for the orange color of carrots. Carotenoids are important food materials and they enter into this discussion by virtue of their capacity to serve as precursors for retinol and its related analogs. Specifically, beta-carotene possesses what is termed high vitamin-A "activity", signifying its capacity to serve as an efficient precursor in this regard. This relationship can be seen in the chemical structures illustrated in the figure (3).



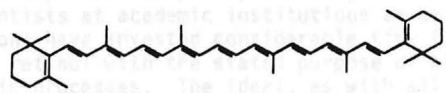
VITAMIN A, RETINOL



VITAMIN A ALDEHYDE, RETINAL



VITAMIN A ACID, RETINOIC ACID

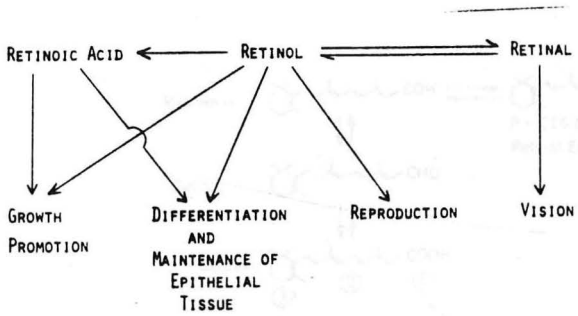


β-CAROTENE

Pawson, BA: JAAD 6:577, 1984 (3)

This observation that substances from a variety of sources can be metabolized into the active vitamin is complemented, as will be seen later, by the fact that vitamin A is metabolized ultimately into several essential compounds which possess diverse activities. Two related compounds, retinol and retinoic acid, are illustrated as well.

The next illustration diagrams the metabolic interconversions which are possible for each compound as well as demonstrating clearly that these retinal derivatives have differening biologic attributes.



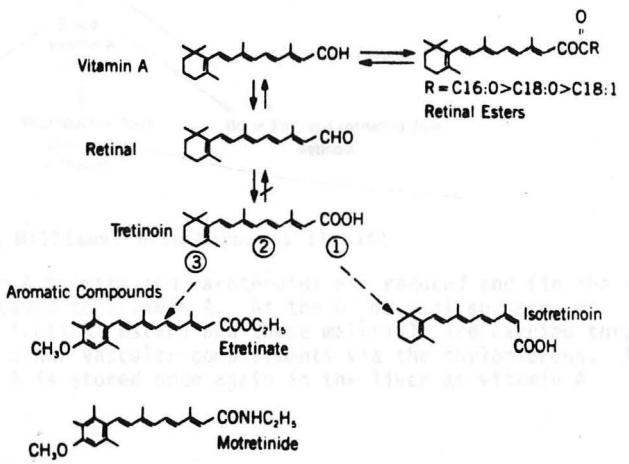
Pawson, BA: JAAD 6:577, 1984

Since the emphasis of this review is dermatologic, I will emphasize that the capacities of retinol and retinoic acid to control the differentiation and maintenance of epithelial tissues. The capacity of retinol and its analogs to control growth, reproduction, and vision will be left to our colleagues in pediatrics, obstetrics, and ophthalmology, at least until the capacity of such drugs to cause untoward side effects becomes unavoidable.

At this point, it is important to preempt the logical flow reminding ourselves that both scientists at academic institutions as well as in pharmaceutical corporations have invested considerable time (money) in investigating analogs of retinol with the stated purpose of altering human physiologic and pathologic processes. The ideal, as with all pharmaceutical enterprises, is to obtain drugs which possess relatively great therapeutic effects in comparison with their intrinsic toxicities. The use of retinol and its analogs is predicated on the observation that the natural materials have important biologic properties.

II. BACKGROUND

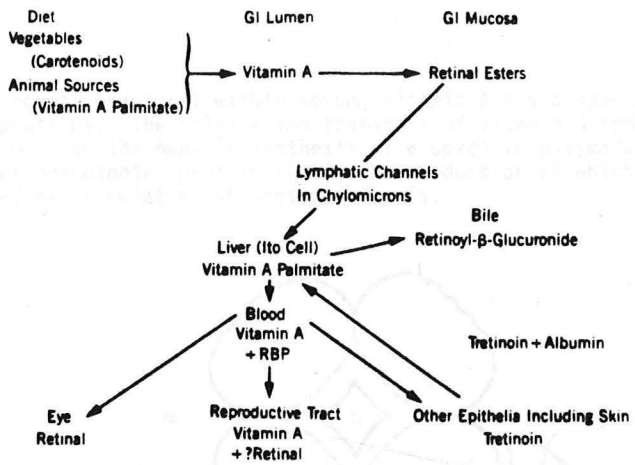
The interconversions of vitamin A with its analogs occurs in the following way (5). As seen in the figure, vitamin A may be converted directly to retinal (the aldehyde) followed by a partially one-way conversion to tretinoin (retinoic acid).



Elias and Williams: Arch Dermatol 117:161 (5)

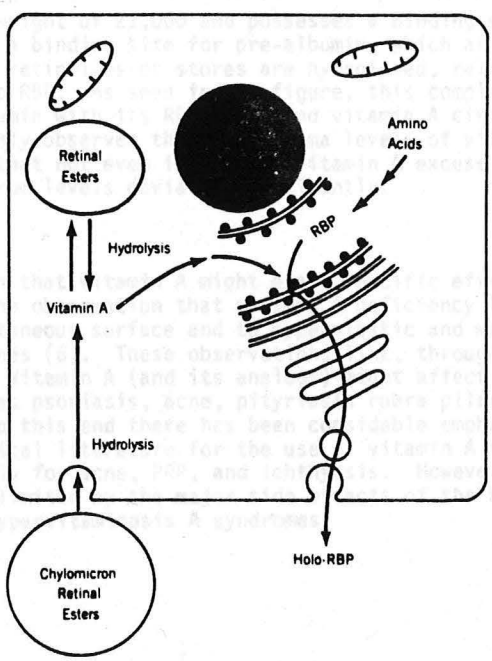
Note that the term tretinoin identified all-trans-retinoic acid. As will be seen later, isotretinoin is all-trans-retinoic acid with the exception that the 13 carbon bond is in the cis position, the compound being referred to as 13-cis-retinoic acid. Note as well that the aromatic compounds possess an unsaturated benzene ring rather than the saturated six carbon ring of the other compounds. Synthetic compounds such as etretinate and others have been manufactured in the search for increased therapeutic advantage.

As seen in the next figure, the common human diet contains carotenoids as vegetable products, the most familiar being beta-carotene and vitamin A from animal sources, the most common being an ester of palmitic acid (vitamin A palmatate).



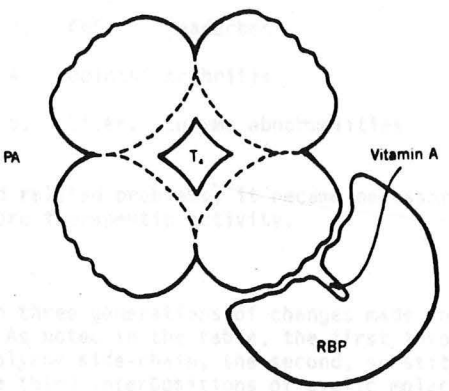
Elias and Williams: Arch Dermatol 117:161

In the GI lumen vitamin A palmite and carotenoids are reduced and (in the case of the carotenoids) cleaved to vitamin A. At the GI mucosal surface, an aldehyde ester is made (retinal ester) and these materials are carried through lymphatic channels and other vascular compartments via the chylomicrons. As you might predict, vitamin A is stored once again in the liver as vitamin A palmatate.



Elias and Williams: Arch Dermatol 117:161

For normal transport within serum, vitamin A has a special family of binding proteins. The release and transport of vitamin A from liver occurs in association with the hepatic synthesis of a specific plasma-binding protein called retinol-binding protein (RBP), the production of which in turn is controlled by circulating RBP-retinol levels.



Elias and Williams: Arch Dermatol 117:161, 1981 (5)

RBP has a molecular weight of 21,000 and possesses a binding site for 1 retinol molecule, as well as a binding site for pre-albumin, which as an aside also binds thyroxine. As retinol ester stores are hydrolyzed, released vitamin A (retinol) is bound to RBP. As seen in the figure, this complex of four molecules of pre-albumin with its RBP and bound vitamin A circulates within the plasma. It is commonly observed that the plasma levels of vitamin A are so strictly controlled that not even in massive vitamin A excess or in severe deficiency do the serum levels deviate significantly.

Biochemistry

The first notion that vitamin A might exert specific effects on epithelial tissues arose from the observation that vitamin A deficiency led in man to kyperkeratosis on cutaneous surface and to hyperplastic and metaplastic changes in the mucous membranes (6). These observations link, through dermatologists, the possibility that Vitamin A (and its analogs) might affect disorders of keratinization such as psoriasis, acne, pityriasis rubra pilaris (PRP) and Darier's disease. To this end there has been considable emphasis in the classical dermatological literature for the use of vitamin A for therapeutic purposes, particularly for acne, PRP, and ichthyosis. However, the use of vitamin A itself is limited by the major side effects of the hypervitaminosis syndrome including Hypervitaminosis A syndromes.

ELEMENTS OF THE
HYPERVITAMINOSIS A SYNDROME

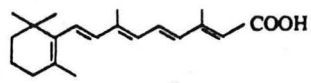
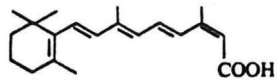
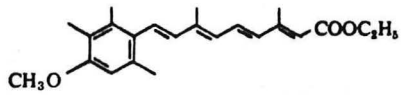
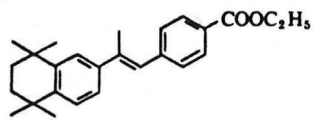
1. Skin: Erythroma, Dryness, Peeling, Cheilitis
2. Hair: Alopecia
3. CNS: Headaches
4. Joints: Arthritis
5. Liver: Enzyme abnormalities

Because of these and related problems, it became necessary to develop drugs with less toxicity and more therapeutic activity.

Chemistry:

There have been three generations of changes made in retinol to produce effective analogs. As noted in the table, the first involved manipulation of the polar end and polyene side-chain, the second, substitutions in the terminal ring system; and the third interpositions of cyclic molecules in the polyene chain. You will note the corresponding changes in the table (6).

Table I. List of a series of retinoids with different chemical structures*

Retinoid	Therapeutic indices of some retinoids: Chemical structure	Lowest dose causing hypervitaminosis A (mg/kg)	Anti-papilloma effect ED 50 (mg/kg)	Therapeutic index
all-*trans*-Retinoic acid (tretinoin)		80	400	$\frac{80}{400} = 0.2$
13-*cis*-Retinoic acid (isotretinoin; Accutane)		400	800	$\frac{400}{800} = 0.5$
Aromatic retinoid (etretinate; Tigason)		50	25	$\frac{50}{25} = 2.0$
Arotinoid ethyl ester		0.1	0.05	$\frac{0.1}{0.05} = 2.0$

*The therapeutic index, as well as the dose necessary for an antipapilloma effect, varies markedly between the various retinoids. The therapeutic index was defined as the ratio between the lowest daily intraperitoneal dose causing, in a 14-day study, a defined degree of hypervitaminosis A and the dose given intraperitoneally once a week for 2 weeks causing 50% regression of papillomas.

Note the increasing therapeutic index, rising from 0.2 to 2.0 from tretinoin to etretinate. Note as well, that there is as yet no therapeutic advantage for the third generation even though the arotinoid ethylester is 500-fold more active (in both respects).

TABLE: RETINOID GENERATIONS

First - manipulation of the polar end and polyene side-chain

a. esters, amides, alderhydes, ether amines
b. chain modification: isotretinoin

Second - replacement of the cyclic end with substituted and nonsubstituted ring system

a. etretinate

Third - cyclization of the polyene side-chairn

a. arotinoid ethyl ester

III. EPIDERMIS

A. Structure and Function

It is important to emphasize the concept that skin, in particular its outer portion or epidermis, presents an interface. The primary function of epidermis is to establish and maintain a semipermeable barrier to molecular exchange between man's internal and external environments, and the anatomical location of that barrier is the outermost surface of epidermis, termed the stratum corneum (7). As emphasized six years ago in my first Grand Rounds, it has been recognized with increasing frequency that significant chemical intrusion may occur from that external environment. Hexachlorophene penetrates intact skin in significant amounts when used for its antibacterial capacity (8) as does gamma benzene hexachloride when used as a scabacide (9). Both have the capacity to produce serious toxicity, particularly in children. Furthermore, for some agricultural workers the percutaneous absorption of choline esterase inhibitors must be monitored carefully to prevent serious atropine-like toxicities (10). By contrast, physicians have taken advantage of controlled-rate percutaneous sensitivities to deliver drugs in a selective fashion through the skin for the treatment of systemic diseases, a prime example being cardiac vasodilators (11, 12).

Few biologic systems encounter the wide variety of concentration gradients which occur at the skin surface, although there are a wide variety of biological systems in which active transport, passive diffusion, or inhibition of diffusion occurs at an interface. These include erythrocyte permeability, renal tubular excretion and even molecular transport across mitochondria. In a provocative discussion Arndt, et al. discussed the skin as an interface which effectively withstands mechanical, chemical, and biologic insults. In that discusion Arndt recognized that thermo-regulation and the absorption of ultraviolet light also occur at this cutaneous interface (13).

The basic element in the epidermal permeability barrier is the corneocyte. As an aggregate, these individual leaflets form a semipermeable membrane, the stratum corneum, a structure which has a significant impact on systemic homeostasis. Corneocytes have no nucleus and are roughly hexagonal in shape (14), they measure about 30 microns in diameter, giving them a surface area of about 1000 square microns (15). Viewed on end they are one-half micron thick (16). These metabolically inactive cells cover the entire skin surface and as an aggregate control small molecule exchange with the environment. Over time corneocytes, both individually and in small clusters are desquamated from the skin surface. This loss of cells from the skin is compensated for by an obligate process of cellular proliferation and maturation within the underlying viable cell layers beneath, and this entire structure as an aggregate comprises the outer portion of the skin or epidermis.

To maintain the stratum corneum, which is in continuous desquamation, there is a steady-state and rapid proliferation of keratinocytes. The existence of steady-state proliferation, maturation followed by destruction classifies the epidermis along with the erythron, gastrointestinal epithelium and testis as a tissue of continuous renewal.

Embryologically, skin is first identified as two distinct layers at the interface with the yolk sac (17). The outer layer, which is ectodermal in origin, faces into the yolk sac and eventually becomes epidermis. The inner layer, which is derived from the superficial portion of mesoderm, becomes the supporting dermis. Throughout fetal development, the epidermis gradually increases in thickness. During much of this time, complete maturation of keratinocytes does not occur. Even late in the second trimester, the superficial cells at the interface with the amnionic cavity have superficial microvilli. It is felt that the "dynamic" cells account for a significant nutritional uptake into the fetus. At about 160 days of gestation, the stratum corneum develops abruptly. By this time, the epidermis has assumed the form it maintains throughout life. It is bounded on the outside by the environment and on the inside by a basement membrane which is a combined product of keratinocytes and fibroblasts.

Individual keratinocytes are bound to each other by numerous periodic attachment processes or desmosomes (18). It is thought that these structures provide the strength necessary to keep individual keratinocytes attached to each other. Adjacent to the desmosome, cytoplasmic tonofilaments terminate near the surface of the cell, and within the desmosome itself the outer leaflets of adjacent tri-laminar cell membranes fuse to establish a shared portion of cell membrane.

B. Proliferation and Maturation.

To illustrate structural as well as functional attributes of epidermal cells, I have developed an extended analogy which depends upon the analysis of similar attributes among erythrocytes. This analogy begins with definitions. The erythron has been defined as the combined mass of immature and mature erythrocytes. Six years ago I introduced a new word, the keraton, which was defined at that time as the combined mass of mature and immature keratinocytes. This analogy extends farther. Both cell lines are terminal since the cells which perform that tissue's functions are incapable of division. Such terminal cells arise from cell division in a proliferative pool; they may mature while accumulating a specialized protein, and then lose their nuclei in the final step. As functioning cells, both survive for a finite period of time, 120 days for erythrocytes and approximately 14 days for corneocytes, at which time they are destroyed and lost. An important aspect of this analogy is that it allows one to visualize a less familiar tissue, the epidermis (keraton) by comparing it to the better known one (erythron).

C. Sebaceous Glands.

In addition to epidermis, the epithelial cells which cover the skin surface also interact with dermal elements to form the skin appendages. Prominent among these are eccrine glands, hair, and sebaceous glands, the last two structures combined into what is known as the pilosebaceous apparatus. Hair is the product of the pilar portion, and most likely represents a vestigial element, providing what is thought now to be an element of adornment. Sebaceous glands manufacture a complex lipid material which is slowly extruded to the skin surface via the same duct. This stratum figures prominently in acne, a disorder of failed delivery of sebaceous materials.

IV. EPIDERMAL DISORDERS

A. Psoriasis

Psoriasis is an idiopathic hyperproliferative disorder of the epidermis which may be characterized by the accelerated entry of corneocytes into the stratum corneum. Both the proliferative and maturation compartments are greatly enlarged, increasing many times in size. Nucleated cells occur frequently within the stratum corneum, indicating that the accelerated release is associated with incomplete maturation. Each corneocyte, however, may function normally, but as an aggregate, stratum corneum barrier is faulty. Psoriasis treatment consists of the removal of excess corneocytes with keratolytic agents and the inhibition of cell division with drugs and ultraviolet radiation.

Because skin is so accessible, much is known about histopathologic events in psoriasis. In fact, so much is known that dermatologists have largely ignored the possibility that psoriasis may have systemic manifestations as well. Associated with the large increase in the number of cells populating the epidermis there is also an absolute and relative increase in the mitotic index. This observation led earlier investigators to the correct assumption that the most prominent alterations in the skin in psoriasis are an increased rate of cellular replication and incomplete differentiation.

Other important histopathologic observations have been made and some of these have definite clinical counterparts as well. Because of the accumulation of corneocytes, their excessive numbers and incomplete attachment to each other causes them to detach from the skin surface in large aggregates, commonly known as scales. Also prominent among the light microscopic changes seen in psoriasis is a dramatic increase in the number of high dermal blood vessels. Such vessels are dilated and they extend with the dermis through almost to the surface of the skin. This is reflected clinically, as mentioned previously, by fine pinpoint bleeding sites when superficial scale is scraped off the skin surface. Although it has been largely ignored, there is also a significant inflammatory infiltrate in the skin.

The primary clinical lesion of psoriasis is a small, red papule with superimposed scale (stratum corneum). Psoriasis is said to be asymptomatic, but this is frequently not the case. New psoriatic papules have a predilection for change, particularly expansion, and the individual papules may expand or coalesce into large red plaques which are also covered or superimposed with scale. An important clinical feature of psoriasis is that when involved areas are scraped, pinpoint bleeding occurs (Auspitz phenomenon), indicating the close proximity of underlying vessels. Furthermore, the erythema of psoriasis may be compressed out (diascopy). These two features indicate that the erythema of psoriasis results from vasodilitation and that these vessels are close the the skin surface, a conclusion which has been documented in histopathologic specimens. When psoriasis involutes spontaneously it frequently clears at the center of a plaque, leaving an annular ring.

Psoriatic arthritis may occur in 5% or more of patients with psoriasis. Although its existence as a distinct disease entity has been doubted by some investigators, most rheumatologists and dermatologists now accept it as such (19). Part of the confusion has arisen from the wide spectrum of clinical

presentations of psoriatic arthritis, with some patients having seemingly spontaneous remissions and relapses while others pursue a progressive, unremitting course. Moll and Wright brought light to the clinical confusion by classifying their patients into five categories (19):

a) Classical psoriatic arthritis in which the DIP joints are primarily involved.

b) Arthritis mutilans often complicated by digital telescoping resulting from severe osteolysis. These patients often have sacroiliac involvement.

c) Symmetrical arthritis indistinguishable, except for negative serology, from rheumatoid arthritis.

d) Asymmetrical involvement of single or a few small joints. This pattern usually affects scattered DIP, PIP, and MIP joints.

e) Rheumatoid spondylitis.

Leonard, McDuffy and Rogers described 77 consecutive hospitalized patients at the Mayo Clinic during six months in 1976 and 1977 (20). They obviously observed a higher percentage of patients with arthritis than would be expected in the general population of psoriasis patients since hospitalized patients have more severe psoriasis and since arthritis occurs more frequently with severe psoriasis. Despite this, their data provides perspective into the clinical presentation of this disorder. Joint disease occurred in 40 out of 77 patients (52%).

Pathogenesis of Psoriasis: The most obvious defect in skin involved with psoriasis is accelerated keratinocyte proliferation. This defect which was suggested by the significant increase in the epidermal compartment size, the excessive amount of scale which is lost by patients, and the increased number of mitoses, was clearly established by Van Scott and his co-workers in 1963 by the observation of increased uptake of ^{3}H-thymidine by keratinocytes within the lesions of psoriasis (21). Since that time numerous reports have documented the increased proliferative behavior of psoriatic epidermal cells compared with normal epidermal cells (22-24). When psoriatic skin is removed from patients for in vitro studies, however, most investigators find no difference in proliferative rates (25,26). Harper, Rispler and Urbanek, however, have observed in their own in vitro skin organ culture system that both lesional epidermis and normal appearing skin from patients with psoriasis exhibit increased DNA uptake when compared with normal controls (27). This is consistent with the observation of Marks (28) and others (29,30) that in vitro thymidine uptake is increased in psoriasis plaques as well as normal appearing psoriatic skin when compared with normal controls. This is not a trivial question since it has yet to be determined whether accelerated proliferation as seen in psoriasis is inherent to the epidermal cell (31,32) or results from the local environmental impact of vascular supply (33) or inflammatory insults.

Psoriasis Therapy: The selective treatment for psoriasis depends on several factors: extent of involvement, patient age, patient expectations, and the resources available. There is no compelling reason to treat a patient who is found incidentally to have psoriasis during an examination and who does not desire it. Patients who request help may receive any of several treatment modalities. The major categories of treatment are listed in the table.

PSORIASIS THERAPY

1. Topical Corticosteroids.
2. Ultraviolet Light
3. Tar and Ultraviolet Light
4. Psoralens and UVA (Photochemotherapy or PUVA)
5. Anthralin (Dithranol)
6. Chemotherapy: Methotrexate, Hydroxyurea, Imuran (Mycophenolic Acid, Azaribine)

Not all of these treatments have the same popularity with the F.D.A. that they have with practitioners. Of the drugs used in systemic chemotherapy, only methotrexate is approved for psoriasis; hydroxyurea and Imuran are available since they are approved for other uses; and mycophenolic acid and Azaribine are not available, although Azaribine was approved at one time but was withdrawn later. In addition, there are several unconventional or experimental modes of treatment.

B. Acne:

Acne is the most common skin disorder, affecting as many as 85% of the American population at one time or another during their lives. Acne is also the single most frequent reason for patient visits to the dermatologist, representing 25% of all encounters (34). The high prevelance of acne among adolescents is quickly confirmed by visiting high school classrooms, where more than half of all students may exhibit pustules, comedones, and cysts. Under such circumstances, a cynical observer of modern medical practice might insist that an affliction that regularly affects a majority of individuals, exhibits spontaneous remissions, and rarely produces direct functional impairment should be defined as a "normal" process, rather than an "abnormal" one. But when seen from the perspective of the disabled patient, acne satisfies all requirments for definition as a disease. Thus, based on the distress of those who seek medical attention, all dermatologists will attest to the conclusion that for many individuals, acne vulgaris is a devastating disease, producing unimaginable morbidity.

The inflamed acne cyst that develops on a patient's face results from a sequential process; thus, causes of acne have been postulated for each point in that process. These points of attack are clearly identified by three absolute requirements for the clinical expression of acne -- the presence of sebaceous follicles, the onset of sexual maturation, and sebaceous gland function. In addition, certain secondary factors, such as familial susceptibility, environmental contamination, and bacterial flora, modulate the clinical expression of acne. Each of these six issues have been examined to varying extents so that reviewing the progress made in these areas provides insight by which modern therapeutic maneuvers may be understood. Moreover, several investigational observations have led directly to novel treatments of acne. Obviously, continuing research will probably lead to even more effective treatments.

Considerable work in acne has originated from the hypothesis that lipid metabolism is faulty or abnormally controlled in patients with acne. The most striking observation is that lipid production is absolutely required for acne to develop. Sebum production by sebaceous glands on the forehead of patients with acne is increased significantly over that of control subjects (35); among those individuals with acne, this increase shows a significantly positive correlation with the severity of the acne (36). This is an important factor, but clearly not the only factor, since there is a wide area of overlap between populations with and without acne and among categories of severity in patients with acne. Furthermore, no clear-cut abnormality has been observed in the lipid composition of acne patients. Thus, we must conclude that although increased sebum production correlates with increased severity of acne, no specific lipid abnormality occurs. Consequently, treatment modalities that modulate sebum production may modulate acne, but they will not affect a specific cure.

It has also been proposed that sebum produced in sebaceous glands of patients with acne contributes to acne only after subsequent metabolic alterations. In an enormous effort, investigators have evaluated the capacity of resident bacteria within sebaceous follicles to liberate irritating free fatty acids from sebum triglycerides through bacterial lipases (37). Consistent with this is the observation that free fatty acids produce considerable inflammation when injected directly into the skin (38, 39). Consequently, this mechanism has been postulated as having an important role in producing the inflammatory reaction that occurs around impacted comedones. The major resident bacterium capable of effecting this metabolic transformation is Propionibacterium acnes, a Gram-positive anaerobic diptheroid, which occurs in abundant numbers inside sebaceouse follicles (40,41). Strains recovered from patients with acne are more likely to hydrolyse triglycerides which are made up of irritating fatty acids (Table 4). The bacterial lipase hypothesis is particularly relevant in view of the profound effect of tetracycline-derived antibiotics in decreasing P. acne's resident flora, decreasing skin surface free fatty acids, and most importantly, improving acne.

Despite these observations and associations, the derived model is still not complete since the skin surface lipid composition differs minimally between patients with acne and normal control subjects (42).

Recent attention has been focued on the pilosebaceous follicular structure itself, suggesting that it induces what may be the most important process in acne generation -- mechanical obstruction of the gland orifice (43). Early histopathologic studies indicated orifice obstruction is the first observable pathologic event (44). Abnormally keratinized cells of the follicular infra-infundibulum aggregate and distend the chamber to form a mechanical plug behind which sebum, the normal product of the sebaceous gland, is retained. In mature comedones, the impaction grows so large that the cyst wall eventually becomes disrupted (45). When this happens, lipid metabolic products and products of cornification are released into the dermis, producing intense inflammation.

The final common denominator in all cases of acne is inflammation. Those lesions that bother patients and end with scar formation are inflamed. They appear red, swollen, and warm, and are frequently described as painful. Sebaceous gland drainage is inhibited by the blockage, consequently producing the classic characteristics of inflamamtion.

Acne Therapy: Treatment of acne consists of a logical attempt to interrupt the pathogenic process at any or all points in the sequence. In retrospect, acne therapy may be most effectively visualized with this model; in reality, however, various treatment modalities were not all developed with the model in mind. In fact, most acne treatments are used, not because they satisfy a particular rationale, but simply because they work, without producing bothersome side effects. In recent years, dermatological care has gradually shifted from systemic treatment back to the topical modalities with their enormous advantages. High concentrations of the drug may be delivered directly to the anatomical site being treated without introducing significant levels into the body itself. Melski and Arndt recently reviewed topical care for acne (46).

In a recent review of systemic antibiotic usage in treating acne, tetracycline, oxytetracycline, and chlortetracycline were the overwhelming favorites (47). Tetracycline is effective in the majority of patients and is relatively safe (48). The respondents used in descending order erythromycin, demeclocycline, minocycline, lincomycin or clindamycin, and doxycycline. Initial interest in lincomycin and clindamycin disappeared after their association with pseudomembranous colitis was confirmed (49). Investigators concluded that each systemic antibiotic was effective in treating acne, but that systemic clindamycin and lincomycin should not be used because of their potential toxicity (47).

Fortunately, the advent of topical antibiotics provides some alternatives to the oral use of antibiotics. Tetracycline and clindamycin may now be purchased directly as topical agents; erythromycin is still compounded for topical use. These topical antibiotics satisfy the goal of delivering less drug in high concentrations to the treated site. They are effective and relatively free of side effects (50-52).

Vitamin A acid (retinoic acid) when applied topically alters both proliferation and differentiation of the skin (53). In view of the possibility that aberrant keratinization at the infra-infundibulum may be a requisite step in the generation of acne lesions, it is felt that the beneficial effect is somehow related. Consequently, topically applied vitamin A acid has assumed an

important place in the treatment of acne and has been shown to be effective (54). Benzoyl peroxide, which is also an effective treatment for acne, exhibits a potent antimicrobial effect (55) and results in a significant decrease in free fatty acid excretion to the skin surface. Investigators presume that these two effects are related, and that they in turn are responsible for the effectiveness of benzoyl peroxide in treated patients (56).

In summary, acne vulgaris is primarily an inflammatory disorder of facial pilosebaceous structures. Acne expression depends on sexual maturation and is the culmination of a serial process - pilosebaceous orifice obstruction, sebum production, enlargement of the infra-infundibulum to form a comedo, and the eventual development of inflammation. Effective therapy, which blocks the process at one or several steps, is now available for all but the most stubborn cases. Thus, physicians can offer those patients with this scarring and potentially debilitating disorder an optimistic outlook.

C. Epidermal Cell Carcinomas

It is recognized that human skin which recieves ultraviolet radiation on a chronic basis from either natural sunlight or from artificial sources will develop degenerative changes. These changes include premature ageing and a propensity to develop skin cancer. Epidermal cancers like all other neoplastic growths will occupy space, and in so doing they distort the normal, or at least the expected, anatomical features of the skin surface. This represents one reason why mortality and morbidity rates are so low for most cutaneous cancers, a reason which relates to visibility. It is not possible to recognize a carcinoma of the lung or bowel in its early phases, but to fail to recognize a small tumor in the skin would be nearly impossible. Moreover, the examination of a patient with cutaneous malignancy quickly demonstrates the utility of "regional distributions". Perhaps for no other skin disorder is this so apparent, reflecting the almost invariant pathological relationship between sunlight and skin cancer. Human skin cancers occur most often on the head, neck, hands, and arms, areas of maximal sun exposure. Most common varieties of skin cancer are the basal cell carcinoma, squamous cell carcinoma and melanoma.

Basal cell carcinomas may exhibit a variety of clincical features: cystic tumors, superficial ulcers, scars, scaling plaques, or even pigmented nodules which resemble the malignant melanoma. In contrast, squamous cell carcinomas usually appear as keratotic nodules or as an ulcer with wide, indurated borders. The third common cancer of epidermal cells, the malignant melanoma, while the least frequent of these light-induced skin cancers, is by far the most aggressive. Melanomas do not show the striking predilection for light-exposed skin, but there exists excellent epidemiologic evidence to support an important role for sunlight in the development of this malignancy of pigment-forming melanocytes. Three distinct clinical forms are characteristic of melanomas: lentigo maligna, superficial spreading melanoma, and nodular melanoma.

All epidermal cell tumor types are defined as malignant because they grow without control, although the first two are very infrequent to metastasize. Their treatment has depended mostly on destruction: chemically, surgically, or with x-ray. The epidermal neoplasms are introduced as clinical entities at this

point because the retinoids may, in fact, have some relationship to their treatment.

D. Pityriasis rubra pilaris (PRP):

PRP is a cutaneous disorder characterized by a clinical feature of accelerated epidermal proliferation as well as large increases in both proliferative and functional compartments. Clinically one observes a generalized erythroderma which begins with follicular accentuation and eventually expands to involve virtually the entire skin surface. Particularly important in the differential diagnosis is the observation of desquamating yellowish-orange palmaoplantar hyperkeratosis. This disorder, which is idiopathic, affects persons of all ages and races and nationalities. Its clinical course is unusual in that there is great variation in the duration, but most patients with the disease will spontaneously remit within three years.

Despite the fact that most individuals will spontaneously remit after one to three years, the condition is so severe and disabling that many require aggressive treatment. A variety of modalities have been utilized in this regard, including systemic vitamin A and systemic steroids. The only treatment modality which has been generally successful is the use of systemic methotrexate, which is quite effective in some individuals presumably because of the anti-mitotic capacity of the methotrexate.

V. RETINOID EFFECTS

In cell culture, the effects of retinoids in promoting differentiation are well documented and considered to be important (57-59). It should be noted as well that effects also occur on cell lines which are not of epithelial origin (59).

In vivo test models for Vitamin A effects have been developed to obtain an assessment of therapeutic index (6). Obviously, an assessment of both "benefit" and "toxicity" is required. For benefit, skin papillomas are induced in hairless albino mice with the initiator 7,12 dimethyl-benzanthracine (DMBA) followed by the repeated topical application of the cancer promoter, croton oil. This normally induces epidermal-derived squamous cell carcinomas, but early in the process benign (premalignant) squamous papillomas arise. These chemically induced papillomas have been shown to regress significantly under the influence of retinoids. In an early study Bollag observed that all-trans-retinoic acid, 400 mg/kg once weekly, caused a 51% decrease in the mean diameter of established papillomas whereas control papillomas increased by 25% (60). This became the most important early *in vivo* assay.

The therapeutic index was determined by producing the hypervitaminosis syndrome in panels of mice. The therapeutic index is then defined as the ratio of the lowest dose required to produce the hypervitaminosis A syndrome divided by the lowest dose required to produce a 50% reduction in squamous papillomas (6).

All-trans-retinoic acid was first employed successfully by topical application for acne and then for several related defects in keratinization, including types of ichthyosis. To this day topical retinoic acid is a mainstay in the therapy of acne (61). Additional observations bear watching. Retinoids may affect proliferative diseases (62), diseases in which occur inflammation followed by collagenase activation (63), and most significantly the inflammation of adjuvant arthritis (64).

Mechanism of Action: In 1984 the mechanism(s) of action(s) of retinoids remains pure speculation, although there exists certain working hypotheses. Retinoids may participate as the lipid portion of glycolipid intermediators involved in glycolytic reactions (65,66).

VI. THERAPY

A. Acne

Shalita and his associates summarized their experience with isotretinoin in 1983 (67). They concluded that isotretinoin continues to be successful in the treatment of patients with severe nodulocystic acne who prove to be unresponsive to conventional treatments (including systemic antibiotics). They also extended their concept of its indications to include severe inflammatory acne which is unresponsive to conventional treatments. Note should be made that isotretinoin is used by some physicians for less aggressive acne, despite the possibility of side effects. Shalita also noted that although some patients respond to doses as low as 0.1 mg/kg/dg, there may be a more rapid recurrence associated with discontinuing the lower doses. They reported that the persistent response, even

after discontinuing the therapy, may be the most remarkable aspect of the therapy with isotretinoin. They emphasized that except under unusual circumstances this drug should be stopped after 20 weeks. When acne recurrences do occur they usually are of milder severity and the response to a second course (usually suggested to be less than 8 weeks) is usually even better.

ISOTRETINOIN SIDE EFFECTS

(Acne: 1.0 mg/kg)
Shalita et al.

Mucocutaneous (up to 90%)

Skin
- Chelitis
- Facial Dermatitis
- Xerosis
- Pruritis
- Desquamation
- Hair
- Photosensitization
- Granulation tissue
- Paronychia
- Urticaria
- Acne Flare

Mucous membranes
- Eye irritation
- Nosebleeds
- Dryness

Inflammation: urethra

Vaginal dryness

CNS

Headache; Paresthesias; Emotional Change; Visual Disturbance; Papilledoma

Pseudotumor cerebri

Muscleoskeletal (16%)
Pain, tenderness, stiffness Muscle and/or joint

Hepatic
Minimal - not stored in the liver

Teratogenicity: 5 patients reported to Hoffman-LaRoche

Most important in terms of the use of isotretinoin therapy for acne is the recent summary report of Strauss et al (68). They reported a blinded study of 150 patients with severe, treatment-resistant, nodulogetic acne who were treated with one of three different dose schedules of isotretinoin: 0.1, 0.5, and 1.0 mg/kg/day. Patients were randomized and then treated for 20 weeks. Follow-up observations were made 12 weeks after discontinuing treatment (32 weeks into the study). Results were monitored in terms of the effect on counted cystic lesions. Note first that all three dosage regimens were associated with a substantial decrease in the number of counted lesions.

Table 11

Cystic Lesion Counts During Isotretinoin Therapy (Strauss et al. JAAD 10:490, 1984)

	Dosage (mg/kg/day)					
	0.1		0.5		1.0	
	Face	Trunk	Face	Trunk	Face	Trunk
Baseline	14	40	12	33	15	39
Week 8	7	24	8	22	7	28
Week 20	3	15	3	10	2	20
Week 32 (12)	1	4	1	6	1	10

Note as well that truncal lesions responded well, although not as completely as the facial ones. Thirdly, there were no significant differences, either during the study or for up to 12 weeks after its conclusion in the therepeutic effects. These data suggested at first that considerably smaller dosages of isotretinoin may be required for the treatment of cystic acne, although the next table shows this not to be true. Note that 42% of the 0.1 mg/kg group required follow-up therapy, whereas only 10% of the 1.0 mg/kg group required such therapy.

Percentage of Patients Requiring Retreatment With Isotretinoin

(Strauss et al. JAAD 10:490, 1984)

Dose of First Course (mg/kg/day)	Percentage
0.1	42%
0.5	20%
1.0	10%

It is obviously not my intention in this internal medicine forum to describe to you or to instruct you in the methods of treating acne, but it is important to present to you those side effects and those complications which may be associated with such treatment and which you may see at times other than when treatment is initiated. As mentioned previously, the use of all retinoids, including isotretinoin is associated with several side effects and from the table it is possible to see the frequency of side effects in the 150 patients treated with the three dosage schedules of isotretinoin. The six most important symptoms are extracted from a larger group of data within the article: chelitis, dry skin, pruritus, epistaxis, bone/joint pain, and sore mouth.

Frequency of Clinical Side Effects in Patients
Treated with Three Dosages of Isotretinoin

(Strauss et al. JAAD 10:490, 1984)

	Dosage (mg/kg/day)		
	0.1	0.5	1.0
Chelitis	77%	90%	93%
Dry Skin	56	88	82
Pruritus	47	36	68
Epistaxis	18	30	53
Bone/Joint Pain	18	24	30
Sore Mouth	13	14	30

Note first that there is a positive association between the percentage of patients suffering such effects with increasing dose, and that chelitis rose from 77% to 93% to include virtually all patients receiving high dosage isotretinoin. Note as well, that dry skin and pruritus were very frequent during this drug trial as was epistaxis. Both bone/joint pain and sore mouth increased progressively in the same fashion. These problems are most frequent and perhaps the most disabling, although all of the symptoms mentioned in the previous study occurred in these patients.

Laboratory studies were obtained on these patients as well, and the table shows the frequency of laboratory abnormalities.

Frequency of Laboratory Abnormalities in Patients Treated with Three Dosages of Isotretinoin

(Strauss et al. JAAD 10:490, 1984)

	Dosage (mg/kg/day)		
	0.1	0.5	1.0
Increased Platelets	4%	11%	8%
Increased SGOT	18	15	18
LDH	25	24	20
T. Prot.	18	4	10
Increased TG	4	11	25
Increased HDL	14	21	17

* 10% change on one occasion

For a determination to be considered abnormal they required a 10% change in one value on one occasion. For all of the abnormalities in the first two groups, platelets, SGOT, LDH, and total protein, there was no dose-dependent increase in the frequency of these abnormalities, and when the data were examined by absolute values it was observed that these were simply spurious alterations.

Changes in triglycerides and the high density lipoproteins were substantial.

Mean Blood Lipid Determination Before and at the End of Isotretinoin Therapy

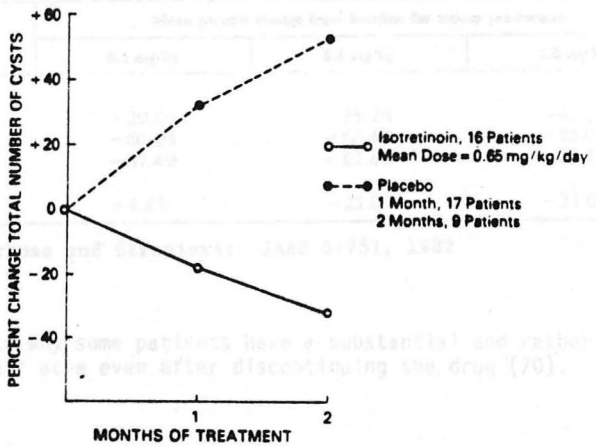
(Strauss et al. JAAD 10:490, 1984)

	Dosage (mg/kg/day)		
	0.1	0.5	1.0
Triglycerides (mg/dl)			
Before	96	102	93
Week 10	104	176*	169*
Cholesterol (mg/dl)			
Before	180	181	173
After	190	182	207*
HDL (mg/dl)			
Before	47	48	46
After	43	43	40*

* $P < 0.01$

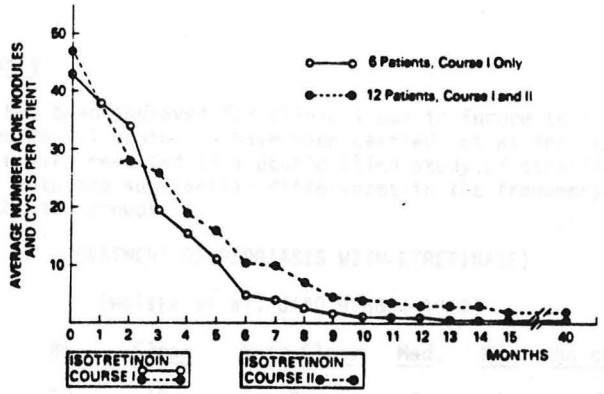
Most consistently and perhaps most importantly there occurred a substantial increase in serum triglycerides, an increase which was significant for the 0.5 and 1.0 mg/kg/day schedules, rising from 102 mg/dl to 176 mg/dl in the intermediate group and from 93 to 169 in the high dose group. Likewise, there was a significant increase in serum cholesterol, rising from 173 to 207 in the high treatment group, and an interesting decrease (slight, but clearly significant) in HDL for the same high dose treatment group. These changes in blood lipids when observed in the past have been felt to be significant, particularly in treatment protocols for diseases other than acne. Since cardiovascular disease is quite infrequent in patients usually treated for acne, and since the treatment for acne as normally given, lasts only up to 6 months, it is not felt that these changes will limit the use of isotretinoin for this illness. Furthermore, it has been observed in other studies that the blood lipid determinations return to normal over time after treatment is discontinued. It is, therefore, the conclusion of this follow-up, long-term double blind study that, in fact, isotretinoin is indeed effective in the treatment of severe cystic acne, and that with appropriate care the therapeutic advantage is substantial.

Peck and his associates have reviewed a more recent study of isotretinoin versus placebo in the treatment of cystic acne. As noted in this figure, there was a substantial difference in the number of acne cysts between the placebo and the isotretinoin groups (69).



Peck et al.: JAAD 6:735, 1982

Moreover you can see that in the treatment group, there is a significant decrease in the average number of acne nodules and cysts per patient (69).



Peck et al.: JAAD 6:735, 1982

This study was complemented by a parallel study in which Strauss and Stranieri determined the changes in long-term sebum production from the isotretinoin therapy (70). There was great variabilty among the patients in the time required for the return of normal sebaceous gland activity after discontinuing isotretinoin therapy.

Daily dose of isotretinoin	Mean percent change from baseline for sebum production		
	0.1 mg/kg	0.5 mg/kg	1.0 mg/kg
Treatment time (wk)			
1-2	−20.8%	−25.2%	−42.3%
5-6	−60.0%	−66.4%	−85.0%
11-12	−67.4%	−82.4%	−88.3%
Posttreatment (wk)			
7-8	−4.8%	−25.0%	−35.0%

Strauss and Stranieri: JAAD 6:751, 1982

This would indicate why some patients have a substantial and rather permanent improvement of their acne even after discontinuing the drug (70).

B. Psoriasis

Etretinate has been approved for clinical use in Europe to treat psoriasis, and several experimental protocols have been carried out at institutions in the United States. Wolska reported in a double-blind study of etretinate to treat psoriasis (71). Note the substantial differences in the frequency of improvement in the two groups.

TREATMENT OF PSORIASIS WITH ETRETINATE)

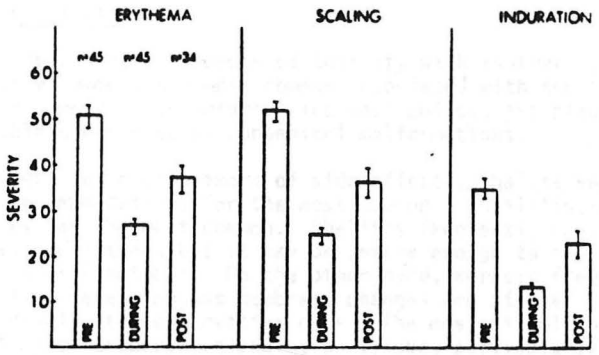
(Wolska et al. JAAD 9:883, 1983)

Therapy	No.	Clear	Near Clear	Med.	Min.	No change
Etretinate	10	0	3	4	2	1
Placebo	18	0	1	2	2	13

Kaplan, Russell, and Lowe conducted a study to determine whether during the expected period of improvement of psoriasis, there were alterations in polyamine levels (72). This is an important issue since polyamine biosynthesis has been observed previously to be increased in patients with psoriasis (73). Moreover, defective polymine biosynthesis has been associated with the induction of carcinomas in some patients, and it is postulated that the capacity to regulate polyamine biosynthesis might be a link to the putative effects of retinoids on carcinogenesis (74). In their study, it was observed that all patients treated with etretinate for either erythrodermic or plaque-type psoriasis had a significant improvement in their skin lesions on doses which range from .4 to 1.25 mg/kg/day. In addition, there was a parallel decrease in polyamines found within the skin during this treatment. This fragmentary report is consistent with the observations of the European investigators that etretinate alone is a significant oral treatment for severe psoriasis, particularly those which involve erythroderma and pustules. In the current study it was observed that virtually all patients with psoriasis improved under treatment, but the length of remission after discontinuing treatment was no longer than approximately eight weeks. There is currently experimental emphasis to combine retinoid therapy with other treatment modalities in psoriasis.

C. Pityriasis Rubra Pilaris and Related Disorders

Goldsmith, Weinrich, and Shupak investigated the capacity of 13-cis-retinoic acid (isotretinoin) to inhibit the expression of pityriasis rubra pilaris (75,76). To that end they evaluated 45 patients from 16 dermatology centers. Individual patients were scored clinically for the severity of disease, based on three parameters, erythema, scaling, and induration, with ranges of 1 to 7. Patients were evaluated before and then during a short-term course of therapy which included isotretinoin, .5 mg/kg/day in two divided doses. Note a temporary improvement.



Goldsmith et al.: JAAD 6:710, 1982

As can be seen, there was a significant decrease in the amount of erythema, scaling, and induration, as seen with treatment. What is also obvious from this figure is that after discontinuing their treatment, the patients had a significant exacerbation of their disease.

Baden and his associates conducted a multicenter study of 13-cis-retinoic acid in both lameller ichthyosis and epidermolytic hyperkeratosis, both of which are hyperproliferative cutaneous disorders (33, 34). As seen in the table, they noted a significant decrease in scaling, erythema, induration, and crusting during their treatment with .5 mg/kg/day of the drug.

Sign	Mean rating* ± standard error of the mean		
	Before treatment	During treatment†	Post-treatment
Scaling	6.13 ± 0.221	2.83 ± 0.195	5.47 ± 0.280
Erythema	3.30 ± 0.414	1.96 ± 0.239	2.76 ± 0.416
Induration	3.22 ± 0.487	1.35 ± 0.119	3.47 ± 0.493
Crusting	3.13 ± 0.484	1.22 ± 0.125	2.47 ± 0.375

Baden et al.: JAAD 6:716, 1982

After discontinuing treatment it is noted once again that values returned almost entirely to the pre-treatment severity levels (33,34). Common to both of these studies is the requirement for continued treatment, which is different from the successful treatment of acne.

D. Side Effects

You will note several aspects of toxicity with isotretinoin. First, side effects are very common, the most common associated with the skin surface, being reversible and simply a discomfort. The most ominous are pseudotumor cerebri and the possible occurrence of congenital malformations.

With respect to the treatment of side effects, Shalita and his associates have several recommendations for the most common. Cheilitis, xerosis, and pruritus are by far the most common. Chelitis frequently does respond well to simple topical emoliation, but it may be severe enough to cause the discontinuation of treatment. On the other hand, xerosis frequently responds to most conservative care. Mucous membrane changes are similar to the skin changes and respond normally to conservative care. The most disabling toxic effect can be the formation of exuberant granulation tissue, particularly in areas of acne cysts. The most dramatic, however, is the exacerbation of acne, sometimes with seemingly violent flares. This process usually occurs early in the course of therapy.

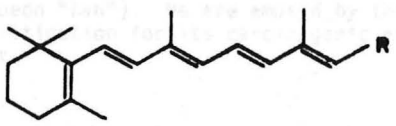
Particularly problematic with respect to the possible toxicity of isotretinoin in long-term trials is a report by Ellis and his associates (52). This paper is of importance, not only because of the observed skeletal abnormalities, but because it demonstrated some of the systemic persistent disorders in which treatment has been attempted with this drug. Diseases included lamellar ichythyosis, Darier's disease, and palmar plantar keratosis. They observed that after one year of isotretinoin treatment, six of the eight patients had small but unequivocal skeletal hyperostosis and five of the patients had multiple hyperostosis. On the basis of this report they recommended that patients taking high doses of isotretinoin for long periods of time should be monitored radiographically. This is important in that Vitamin A toxicity in humans in the past has been associated with cortical hyperostosis and periosteal calcification in patients as well as in laboratory animals. Clear confirmation of the delayed onset of this toxic effect in patients treated for long periods of time , particularly those that are painful or symptomatic should be an indication to reevaluate the risks versus the benefits of continuing treatment with this drug. This is particularly important as isotretinoin is used to treat chronic persistent disorders, and for etretinate which has delayed elimination.

VII. FUTURE THERAPIES

The notion that retinoids might be effective in cancer prophylaxis is derived from several independent lines of reasoning. First, there exists epidemiological associations based on serum levels of vitamin A in patients with cancer as compared with matched populations without cancer. These studies are prospective with respect to the fact that serum was saved from large populations and then assayed for vitamin A in those who developed carcinomas, along with the appropriate control populations taken from the original study population (77,78). The finding that patients with cancer have significantly lower serum vitamin A levels argues only indirectly that vitamin A has a beneficial effect in preventing cancer. And, it has been speculated that there may be beneficial effects in including serum vitamin A in routine health survey programs (79).

Consistent with the capacity to induce terminal maturation of cell lines in tissue culture, etretinate therapy was observed to reduce the degree of squamous metaplasia in heavy smokers (80). Close to cutaneous medicine, 13-cis-retinoic acid was found to be effective in the treatment of four patients with refractory cutaneous T-cell lymphoma (mycosis fungoides) (81). Most interesting with respect to my own interest is the report that retinoic acid stimulates the maturation of mouse killer T-cells in both allogeneic and syngeneic systems (82). Terminal differentiation has been induced in tumor cell lines with retinoids (83,84) and in non-tumor cell lines (85), and the effects of tumor promotors (85,86).

Moon and McCormick have demonstrated that it is possible to inhibit chemical carcinogenesis by the retinoids. In the data to be examined four different retinoid derivatives were used. As seen in the figure, they include retinoic acid and three special derivatives (87).



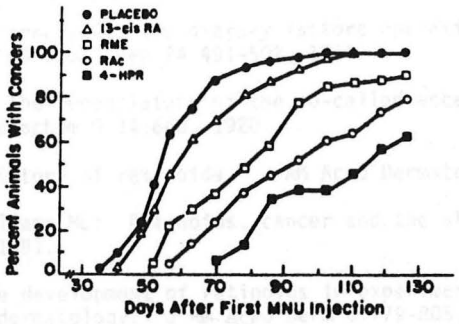
R = COOH = RETINOIC ACID

R = CONH — ⬡ — OH = 4-HYDROXYPHENYL RETINAMIDE

R = CH_2OCOCH_3 = RETINYL ACETATE

R = CH_2OCH_3 = RETINYL METHYL ETHER

Moon and McCormick, JAAD 6:809, 1982



Moon and McCormick
JAAD 6:809, 1982

These materials were given orally to the mice which were then treated with a standard hormonal manipulation. As noted here. the percent of animals with cancers was inhibited significantly by use of the retinoid derivatives.

An interesting question with regard to the possibility that retinoids might be effective prophylactic agents for cutaneous carcinomas relates to the possibility that photoprotection may play a role. Matthews-Roth (88) has demonstrated in mice that while beta-carotine was not effective, canth was. It is extraordinary that canth is the yellowing dye against which FDA litigation is directed for its use as a dietary supplement to promote skin darkening (i.e., pseudopigmentation, or a psuedo "tan"). We are amused by the possibility that a drug which was a target of litigation for its carcinogenic effect may be an effective prophylactic agent.

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