

## Chapter 20

# Accutane: Focus on Psychiatric Toxicity and Suicide

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## 20.1 Introduction

Since early this century, animal research revealed modifications of epithelial structure, such as increased epidermal keratinization and squamous metaplasia of the mucous membrane, under conditions of vitamin A deficiency. The finding that these defects could be corrected by administering vitamin A led to the emergence of vitamin A as an anti-keratinizing factor. The first synthesis of vitamin A fifty years ago opened a new era into the chemical synthesis of vitamin A derivatives, collectively known as retinoids.

First synthesized in 1955, Accutane (Ro 4-3780, isotretinoin), a first generation retinoid, was shown to be highly efficacious in the therapy of disorders of keratinization (e.g., Darier's disease, ichthyosis). Peck<sup>1</sup> was the first investigator to demonstrate this drug's value in the treatment of severe acne and in September of 1982, it was approved for use in the U.S. by the Food and Drug Administration (FDA). Accutane is Roche's second biggest seller, generating about \$300 million in sales through the first half of 1998. From 1993 to 1997, prescriptions in the U.S. jumped 52 percent (to 1.5 million).

## 20.2 Mechanism of Action

Acne is due to an interaction of the normal skin bacteria with the patient's abnormal type of sebaceous lipids,<sup>2</sup> and is associated with an increased sebum production and ductal cornification. The acne bacteria, *Propionibacterium acnes*, reside on the surface of the skin in quite high numbers, especially in oil-rich areas. If they colonize the pilosebaceous duct in the presence of comedones (blackheads and whiteheads), then inflammation is likely to be triggered, resulting in papules, pustules and, if inflammation is more expansive, nodules. Although the exact mechanism of the anti-acne action of isotretinoin is unknown, it is unique in its ability to affect—albeit not to the same degree—all the known etiological factors of acne, including reduction of sebum production, lessening of comedogenesis, and the decrease of surface and ductal colonization by *Propionibacterium acnes*.<sup>3</sup>

## 20.3 Metabolism

Isotretinoin is a metabolic product of the dietary vitamin A and provitamin A carotenoids. Retinol (vitamin A) is absorbed from the gastrointestinal tract and metabolized in the liver into retinal. Retinal is then irreversibly oxidized into retinoic acids, which reversibly interconvert into each other. The two isomers (retinoic acid and 13-retinoic-acid) have an identical chemical structure. Isotretinoin and retinoic acid are further metabolized into oxo-isotretinoin and oxo-retinoic acid, respectively, where interconversion again takes place between both metabolites.<sup>4</sup> The elimination half-life of isotretinoin and its 4-oxo metabolite are twenty-nine and twenty-two hours, respectively.<sup>5</sup>

## 20.4 Adverse Effects of Accutane

Over the years, Accutane has proven its excellence in the treatment of severe, recalcitrant acne. However, it is associated with a long list of side effects that are frequent, varied, and, at times, severe. In clinical trials involving 523 patients, at least one adverse reaction occurred in over 90 percent of patients. The Adverse Drug Reaction Reporting System (ADRRS) of the American Academy of Dermatology was organized in 1980 to facilitate the reporting of new, unusual, or severe reactions to drugs. Between October of 1982 and June of 1985, the ADRRS received 123 reports of suspected adverse drug reactions (ADRs) to isotretinoin. Ninety-three of these reports (twelve reports represented remote association, eighteen showed incomplete information) represented 7 percent of all reports to the ADRRS for all drugs during this period.<sup>6</sup>

The most commonly occurring adverse reactions are those involving the skin and mucous membranes, which occur in

all patients treated with Accutane. Most common among this class include facial erythema, xerosis, minor nosebleeds, dry mucous membranes, dry scalp and hair, cheilitis, conjunctivitis, dry skin, and pruritis, which can occur within forty-eight hours of starting therapy. Other side effects reported include skin fragility, pyogenic granuloma-like lesions and epidermal blistering, paronychia, and alopecia.<sup>6</sup> Gastrointestinal intolerance occurs in 20 percent of patients treated.<sup>6</sup> Muscular or joint pain are quite common with Accutane use. Myalgia and arthralgias—which usually abate when the medication is discontinued—occur in 16 percent of patients treated.<sup>7</sup>

Blepharitis and conjunctivitis associated with Accutane use were recognized well before its marketing. Corneal opacities and acute myopia have been reported in government publications and in the ophthalmologic literature. Other ocular reactions include optic neuritis, cataracts, decreased night vision, blurred vision and photosensitivity. Pseudotumor cerebri (PTC) and headaches are also associated with the drug. In common with other retinoids at pharmacological doses, Accutane causes elevation of serum lipids, particularly triglycerides.

## A. Hypervitaminosis A

Vitamin A is an essential factor in physiological growth, visual function, epithelial-cell differentiation and reproduction, and is believed to exert its influences at the DNA level, where it plays an important role in regulating transcription of a number of genes.

Isotretinoin, being an analog of vitamin A, shares many of the side effects experienced with vitamin A. Vitamin A (retinol) is ingested in the diet as retinyl esters, which are transported to the liver and hydrolyzed in hepatic parenchymal cells. Excess retinol is converted to retinyl esters again and stored in the liver. Retinol binds to retinol binding protein (RBP). When the amount of vitamin A present exceeds the capacity of RBP to bind to it the excess retinol binds to lipoproteins and, in this form, it has toxic effects.<sup>8</sup> Hypervitaminosis A is the condition resulting from an excess of retinol in the body.

There are two types of hypervitaminosis A—acute and chronic. Acute hypervitaminosis A results from ingestion of a very high dose of vitamin A over a short period of time. Typical symptoms include bulging fontanels in infants and headache in adults, nausea, vomiting, fever, vertigo, and visual disorientation. Peeling of the skin may also occur. Chronic hypervitaminosis A is more common than the acute form and results from continued ingestion of high doses for months or even years. Symptoms include anorexia, dry itchy skin, alopecia, increased intracranial pressure, fatigue, irritability, somnolence, pronounced craniofacial and occipital edema, skin desquamation, fissuring of the lips, pain in the legs and forearms, neurologic disturbances, and lethargy. Elevated blood lipids are also common.

## B. Psychiatric adverse events

Vitamin A intoxication—resulting in generalized, as well as central nervous system (CNS) symptoms—was first alluded to in 1856 by Elisha Kane,<sup>9</sup> the arctic explorer. He recorded symptoms of vertigo, headache, drowsiness, and irritability following ingestion of polar-bear liver, which was later found to contain a high concentration of vitamin A. Over the succeeding 140 years, case reports of the occurrence of acute schizophrenia or remitting psychosis associated with either hypervitaminosis A<sup>10,11,12</sup> or vitamin A deficiency<sup>13</sup> have appeared in the literature.

In 1972, Restak<sup>14</sup> reported a case of toxic psychosis in a patient following vitamin A treatment (50,000 IU 2–3 times daily) for acne, which required hospitalization. About six months after initiating vitamin A therapy, the patient experienced the onset of prolonged depression, bouts of elation alternated with despondency, disturbed sleep, insomnia, and loss of appetite. Twelve months later, while on holiday, she became more agitated and depressed, and lost weight. She also developed blurred vision, hyperacusis, vertigo, strong feelings of ego alienation, and lethargy. Following psychiatric referral, total remission occurred over six months of close observation and antidepressant therapy. The authors cautioned against “the use of the vitamins as preventatives for such benign entities as acne.”

In 1992, a case report described a patient, with no previous psychiatric history, who presented a one-year history of depressed mood and poor concentration.<sup>15</sup> Medication included only a multivitamin preparation of 25,000 IU of vitamin A per day, for two years. Hamilton Depression Ratings confirmed full cessation of depressive symptoms after stopping treatment. Other reports of lethargy, loss of interest in surroundings, insomnia, listlessness, profound daily fatigue, anorexia and irritability, in association with vitamin A, have been documented.<sup>16–20</sup>

## C. Pseudotumor cerebri

First described by Gerber,<sup>21</sup> pseudotumor cerebri (PTC or benign intracranial hypertension) has long been associated with vitamin A administration.<sup>22,23</sup> PTC is accompanied by symptoms such as papilledema, vision problems, nausea, and severe headaches. PTC occurs in 30–50 percent of patients with hypervitaminosis A<sup>24</sup> and is characterized clinically by three criteria:<sup>25</sup> (1) Neurologic and ocular symptoms and signs of increased intracranial pressure, which may include headache, nausea, transient visual obscurations, sixth-nerve palsies, and papilledema; (2) radiologically demonstrable

normal or small-sized cerebral ventricles; and (3) elevated cerebrospinal fluid. PTC has been indicated in isotretinoin therapy.<sup>26,27</sup> The retinoid, etretinate,<sup>28</sup> and combination therapy with tetracyclines may increase the risk for it occurring.

### ***Wagner v. Roche Laboratories, decided November 13, 1996***<sup>29</sup>

A consumer brought a products-liability action against Roche, alleging that the defendant failed to adequately warn of the association of Accutane with PTC and of the dangers of concomitant use of Accutane and certain antibiotics such as Minocin (minocycline), a tetracycline derivative. Appellant was prescribed Accutane on November 8, 1982, for acne, along with Minocin (the patient had been taking Minocin prior to receiving the Accutane). Six weeks later, the appellant was diagnosed by the neurologist as having papilledema and PTC. Steroids were prescribed to treat the PTC and, as a result, the appellant experienced avascular necrosis. Appellant underwent several surgeries to replace both hip joints and a shoulder joint. On August 2, 1991, appellant settled her malpractice suit against her dermatologist for \$185,000. In February, 1992, the appellant instituted an action by refiling her complaint against Roche. The appellant's theory of recovery at trial was premised on her presentation of expert testimony that (a) "Accutane is so similar chemically to vitamin A that appellees either were aware, or should have been aware, that Accutane also had the potential to cause PTC," and (b) "that because the two antibiotics the appellant was receiving were both associated with PTC, the combination of the two increased that risk". Dr. Elias, one of the physician investigators who participated in the clinical trials of Accutane, testified that the testing done by the appellees prior to FDA approval, was deficiently designed because it failed to monitor for neurological toxicity, and that because of the similarity with vitamin A, Roche should have predicted the same association of Accutane with PTC. In addition, the appellant presented the testimony of Dr. James O'Donnell, who testified that even in the absence of specific instances of PTC in clinical trials, Roche should have predicted an association and should have warned of this possible effect. Further support for the appellant was a Roche document entitled "Addendum to Schedule 7, Investigational Drug Brochure," dated March 20, 1978, which contains an extensive listing of abnormalities in its "Precautions and Warnings" section. One of the reported associated abnormalities listed in patients with chronic vitamin A intoxication was, "papilledema with increased intracranial hypertension." The same document also stated, "A review of the clinical studies discussed in this brochure indicates that the adverse reactions seen with the use of orally administered Accutane are essentially those of hypervitaminosis A."

## **20.5 Accutane and Depression**

Depression associated with Accutane therapy has, in the past, been described as idiosyncratic; however, increasing reports of depression associated with its use show it is not the rarity it was once considered to be.

### **A. Literature reports**

Between 1982 and 1998, twenty-four cases of psychological distress associated with the use of this drug were reported in the literature. Most of these cases reported the subsequent emergence of depression with features similar to that of hypervitaminosis A.

In 1983, one year after market release,<sup>30</sup> a reported 5.5 percent (six out of 110) of patients with acne experienced depressive symptoms—manifested by malaise, crying spells, and forgetfulness—within two weeks of commencing isotretinoin therapy. Meyskens<sup>31</sup> also noted similar psychological changes in patients with cancer treated with 3 mg/kg/d isotretinoin. The ADRRS of the American Academy of Dermatology, received reports of 104 suspected adverse reactions to isotretinoin between October 1982 and June 1985, of which CNS disorders represented 22.1 percent (twenty-three out of 104), second to skin and mucous membrane reactions (27.9 percent) (twenty-nine out of 104).<sup>6</sup> These CNS reactions included headache, depression, dizziness, and personality disorder. Scheinman<sup>32</sup> reported that 1 percent of patients treated developed depressive symptoms with oral isotretinoin, with symptoms severe enough to interfere with their normal functioning. In this particular report, the relationship of depression to isotretinoin therapy was confirmed by rechallenge. This was also confirmed by Villalobos' patient, who reported the onset of hallucinations and paranoia on day eleven of isotretinoin therapy, which subsided when drug intake was stopped, but recurred shortly after resumption of isotretinoin.<sup>33</sup> In Italy, Gatti reported a case of suicide two months after stopping isotretinoin therapy.<sup>34</sup> Bravard described three case reports of depression, where none had a prior history. One of these patients attempted suicide during the fourth month of isotretinoin therapy, and one committed suicide three months after cessation of therapy.<sup>35</sup>

Cessation of depressive symptoms does not always occur upon withdrawal of the drug. Byrne described three patients who presented with severe depression and who required active treatment. In all three cases, the patients' moods improved with antidepressant therapy. Despite the recurrence of one of the patients' acne, follow-up showed no depressive symptoms, confirmed by a score of five on the Hamilton Depression Rating Scale.<sup>36</sup>

### **B. Media reports**

Public concerns about the safety of isotretinoin have been raised in the past. In 1998, reports surfaced in the media associating this drug with suicides (one in Ireland, two in the UK, and two in the USA) and suicide attempts (one in the UK and one in the USA).

### **1. London *Independent***

Ms. Sheila Asprey wrote her own experience in the London Independent of June 30, 1998:

I started the three-and-a-half month course in March [1998]. After two or three weeks, my lips began to feel sore. Four weeks presented a slightly different story. I had developed mood changes which had been denoted as "other less common unwanted effects". By five weeks, I was almost oblivious to how aggressive and argumentative I had become. By the sixth and seventh week, I was so irrational my partner did everything to avoid confrontations. I became depressed and would sit alone, unwilling to discuss everyday minor problems, which to me had become insurmountable. I don't remember opening the bottle of wine or swallowing a bottle of pills. At the hospital, nobody expected me to live. For three nightmarish days I was comatose and hallucinating. When I recovered, my memory was severely impaired. I know positively that my treatment was responsible for my depression. I came off the drug six weeks ago and I can feel myself getting better everyday. I'd rather live with it [acne] than risk any other treatment.

### **2. The *Star-Ledger***

The New Jersey newspaper, the *Star-Ledger*, on Monday June 29, 1998, told the tragic story of Christopher Tremain, a nineteen-year-old Lake Hopatcong student, who committed suicide in June 1997, six weeks into his treatment of Accutane for his acne. Within a month after starting Accutane, his moods were up and down, he lost his appetite, and slept a lot. Neither he nor his family had any prior history of depression. A Harvard Professor, Jerry Avorn, aired his views that the post-marketing monitoring system is inadequate, with a haphazard collection of spontaneous reports and an understaffed FDA. The article proposed that the FDA, in the fiscal year 1998, would spend just \$10 million on drug surveillance, in comparison with \$156 million to evaluate new drugs. The FDA stated they were prevented from making any further moves about Accutane, as although there had been an association between Accutane and depression; there was no indication of a cause.

### **3. The *Advocate***

In the *Advocate*, dated June 8, 1998, Amanda Callais told of how she survived a suicide attempt during treatment with Accutane. Amanda started her five-month-long Accutane therapy in September of 1997. With no prior history of depression, she went through a personality change. A high school sophomore, her grades dropped dramatically, she stopped eating, and slept a lot. She alienated herself from friends and family. Her medical records reflect she became moody, angry, and belligerent. She finally attempted suicide in November of 1997, after which she was put under the care of psychiatrists. She immediately stopped taking the Accutane, and her psychiatrist began to notice an improvement in her mood. In April, she was discharged from care and her psychiatrist noted her depression was "resolved" and the Accutane "may have provoked (her) depression."

## **20.6 Accutane and Suicide in Adolescents**

Four case reports of adolescents who were prescribed Accutane for acne, and subsequently committed suicide are presented. In each case, a detailed chart review was performed, and significant family members were interviewed. Standard scientific rules were used to determine whether a causal relatedness to Accutane could be established, and in each case, at least a probable causal relatedness was determined. Implications with regard to patient and family warnings, and the adequacy of labeling are discussed.

Accutane is a retinoid drug which has been available in a number of countries for at least twenty years, for the treatment of nodular cystic acne. The exact mechanism of action for the anti-acne property is unknown, but Accutane is thought to interfere with fatty acid production which can damage the oil glands and reduce the amount of oil the skin produces. Accutane is indicated for the treatment of severe and scarring nodular acne not responsive to other forms of treatment, but despite its significant serious adverse effect (SAE) profile, more than 90 percent of females treated with Accutane did not have severe cystic acne (FDA).

As a retinoid, adverse effects characteristic for that drug class appeared with early clinical studies, and include: increased pressure in the brain (leading to severe and persistent headaches), damage to the liver, pancreas, and intestines, hearing problems, decreased night vision, increased levels of cholesterol and triglycerides, allergic reactions

including hives, swollen face or mouth and trouble breathing. Additional side effects can include: dry and chapped lips, dryness of nose/nosebleeds, irritation of the eyelids and eyes, hair thinning, and increased sensitivity to sunburn.

Birth defects were seen early on, and presented a particular problem of warnings in that the drug was intended for use precisely in that demographic group with a high incidence of pregnancy. With careful warnings, and patient and physician understanding, the frequency of birth defects due to Accutane has been kept relatively low, although a significant number of children continue to be born each year with severe birth defects causally related to Accutane. While the warnings against birth defects, a serious and severe adverse event of known causation, has been aggressively addressed, the serious and severe neuropsychiatric adverse effects of Accutane have only recently begun to receive warnings. These include depression, psychosis, suicide ideation, suicide attempts, and suicide.

## **A. Case studies**

I have had the opportunity to review the medical records, and in some cases to examine, a number of these potential cases, and report here on four instances of depression and suicide at least probably associated with Accutane use.

## **B. Methods**

In each case, as complete a set of medical records for each patient were reviewed. This included, whenever possible, specialty consults, including neurology, psychology, and neuroradiology. Police reports, autopsy documents and other documents were included when available.

Causation was determined using standard methodologies employed universally by the Pharmaceutical industry, the FDA and the CDC. These are adaptations of the rules delineated by Hill, and by Riddell, as described in detail elsewhere. In summary, documents were looked at for the following:

- temporal relatedness,
- pre-existing psychological or medical problems, and
- other medications with neuropsychiatric effects effects.

Causality assessments were expressed in terms of a qualitative probability scale, “definite” vs. “probably” vs. “possible” vs. “doubtful” vs. “unrelated.”<sup>37</sup>

## **C. Substance-induced mood disorder**

A SIMD is “a prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following: depressed mood or markedly diminished interest or pleasure in all, or almost all, activities; elevated, expansive, or irritable mood.”

SIMD should be suspected when there is evidence from the history, physical examination or laboratory findings of either

- the symptoms developing during, or within a month of substance (SSRI) intoxication or withdrawal, or
- the medication (SSRI) use is etiologically related to the disturbance (homicide, suicide).

In addition, for SIMD,

- the disturbance does not occur exclusively during the course of a delirium;
- the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning;
- with depressive features: if the predominant mood is depressed;
- with manic features: if the predominant mood is elevated, euphoric, or irritable;
- with mixed features: if symptoms of both mania and depression are present and neither predominates;

## **D. Clinical summaries**

The medical records in these four cases were voluminous, but a capsule summary is presented for each.

### **1. Case 1**

A seventeen-year-old young man who took Accutane from September 29, 1998 to January 29, 1999 (based on the number of doses available) for cystic acne not responsive to topical and antibiotic treatment. In January, February and

March of 1999, he became increasingly anxious, restless and irritable. During this time, he experienced increased mood swings and abrupt changes in mood including at least one violent outburst. He suffered from an inability to sleep the last two months prior to his death, elevated body heat and rectal bleeding was reported on April 27, 1999. The behavior exhibited while taking Accutane was inconsistent with his behavior before Accutane use and typical the weeks leading up to May of 1999 when he committed suicide by hanging.

## **2. Case 2**

An eighteen-year-old male who took Accutane for an undetermined time. He was diagnosed with ADHD in April, 2000 and began treatment with Adderall. He was an athlete and very involved with school sports. He occasionally used tobacco and alcohol and had previously used marijuana in 2000. On August 11, 1999, he saw a physician for feelings of feeling run down and tired, having no energy, and not wanting to eat. Then on August 21, 1999, he saw another physician for complaints of shortness of breath, sore throat, and fatigue. His symptoms had not improved since his previous visit. The assessment was that the patient appeared sluggish, had a flat affect, was possibly depressed and malnourished due to drug appetite suppression. Medications included Accutane, Adderall and Allegra. On August 28, 2000 the patient was again seen for early morning awakenings, anxiety, jitteriness, and nervousness which the physician attributed to Serevent and Adderall. Serevent was discontinued and Adderall was changed to 5 mg bid. He committed suicide by gunshot to the head on September 9, 2000. The September 9, 2000 toxicology screen was positive for 0.061 percent blood alcohol. Reportedly he had been upset about his relationship with a girlfriend.

## **3. Case 3**

An eighteen-year-old male who received Accutane for acne from April 9, 2000 until his death by suicide on October 31, 2000. Before and during the time he was on Accutane, the patient did not exhibit signs of depression, anxiety, restlessness, or express suicidal ideation.

## **4. Case 4**

A sixteen-year-old male who received Accutane from May 12, 2000 to November 11, 2001. Social stressors included an exceptionally driven and successful brother and the recent breakup of a romantic relationship. He had no prior history of depression. A clinical psychologist evaluated him on 8-01 and documented that, for several months prior, he had experienced depressed mood, reduced motivation and interest, increased irritability, chronic fatigue, sleep disturbance, erratic appetite and suicidal ideation. That same month, the patient's mother reported that he was started on an unidentified antidepressant and then in an August 23, 2001 progress note by Dr. Potvin notes that the patient was switched to Zoloft 20 mg, 1 tab, daily for a short time. By September 5, 2001 Zoloft had already been changed to Celexa 20 mg at night and the patient no longer needed Sonata for sleep. On some unspecified date after September 5, 2001, the patient was prescribed Prozac. Dr. Potvin increased Prozac to 40 mg daily on October 31, 2001 because the patient was not sleeping well at night and he was started on Levaquin for prostatitis. On November 11, 2001 he committed suicide.

## **E. Results**

Using the standard rules of causation, a causal relatedness was established in these four cases of neuropsychiatric effects of Accutane. In the second case, the potential existed for a drug-drug interaction contributing to the suicide.

## **F. Discussion**

Side effects experienced with Accutane (isotretinoin), as described by the manufacturer include irritability, feeling unusually tired, changes in normal sleep patterns, and difficulty breathing or wheezing. Post-marketing reports show that major depression, psychosis, and rarely, suicidal ideation, suicide attempts and suicide may be caused by Accutane. Similarly, side effects experienced with Adderall (dextroamphetamine) may include anxiety or severe nervousness, and changes in mood or behavior, including seeing or hearing things that are not there or being over-focused. For the four patients discussed in this report, we have found that their suicides were constant with an adverse event causally related to Accutane.

Accutane has had a very rocky clinical development and regulatory history. Roche developed Accutane in 1971, but chose not to pursue marketing, perhaps for fear of birth defects. However, in 1982 Roche filed a new drug application, which was approved for the treatment of severe cystic acne which is unresponsive to other treatments. Shortly after marketing, FDA and Roche receive reports of Accutane-related birth defects, and stronger warnings were put in the prescribing information.

## 20.7 Neuropsychiatric Adverse Effects of Accutane

1983 AE Report published that 5.5 percent (6/110) of patients with acne experienced depressive symptoms, manifested by malaise, crying spells and forgetfulness, within two weeks of commencing isotretinoin therapy.<sup>38</sup>

Roche amended Accutane's prescribing information in 1985 under "Adverse Reactions" to state, "The following CNS reactions have been reported and may bear no relationship to therapy—seizures, emotional instability including depression, dizziness, nervousness, drowsiness, malaise, weakness, insomnia, lethargy and paresthesias."<sup>33</sup> Again, in 1986, Roche amended Accutane's prescribing information to state: "Depression has been reported in some patients on Accutane therapy. In some of these patients, this has subsided with discontinuation and recurred with reinstatement of therapy."

A case report (1989) discussed a patient who reported the onset of hallucinations and paranoia on day 11 of isotretinoin therapy, which subsided when drug intake was stopped and recurred shortly after resumption of isotretinoin.<sup>33</sup>

Scheinman et al.<sup>32</sup> reported that 1 percent of patients treated developed depressive symptoms with oral isotretinoin, which were diagnosed by a psychiatrist and which the severity of symptoms interfered with their normal functioning. The relationship of depression to isotretinoin therapy was confirmed by rechallenge.

Bravard et al.<sup>35</sup> published a case report describing three case reports of depression where none had a prior history.

Based on a 1992–94 French study of Accutane's association with depression, French health authorities required Roche (March 3, 1997) to add "suicide attempt" to Accutane's side effects. Roche, however, did not inform the FDA.

The FDA initiated discussions with Roche (May 1997) concerning reports of serious psychiatric disorders associated with Accutane. At that time, the FDA apparently was unaware of the new French warning.

In November 24 1997, Roche received a letter from the Department of Health & Human Services, requesting the following change in the labeling be incorporated to furnish adequate information for the safe and effective use of the drug.

Psychiatric disorder. Accutane has been associated with a number of cases of severe depression, psychosis, suicide attempts, and suicide. Follow-up visits during Accutane treatment should include specific questioning regarding psychiatric signs and symptoms. Patients should be specifically warned to immediately discontinue Accutane use and seek medical evaluation if depression or mood changes occur. These adverse reactions have been reported for patients with and without previous psychiatric symptoms. It is not known whether a history of psychiatric disorder or pre-existing depression increases the risk associated with Accutane. In some of the reported cases, depression has resolved with discontinuation of Accutane and reoccurred with the reinstatement of therapy.

A report of three patients who presented with severe depression requiring active treatment was published by Byrne et al.<sup>36</sup> In all cases, the patient's moods improved with anti-depressant therapy. Despite the recurrence of one of the patient's acne, follow-up showed no depressive symptoms, confirmed by a score of 5 on the Hamilton Depression Rating Scale.

A memo from Kathryn O'Connor, FDA (January 29, 1998) noted, "Given all the pieces of evidence available, it is difficult for me to avoid the conclusion that Accutane can adversely affect the adult human brain in clinically significant ways and that Accutane use is associated with severe psychiatric disease in some patients."

A February 1998 FDA memo concluded that Roche "had not acted in good faith to truly and accurately answer questions relating to Accutane use in women and pregnancy exposure." The memo recommended "active consideration of removal of Accutane from the market." The memo also concluded that, "Given all the pieces of evidence available, it is difficult to avoid the conclusion that Accutane can adversely affect the adult human brain in clinically significant ways and that Accutane use is associated with severe psychiatric disease in some patients."

The FDA required Roche (February 25, 1998) to add the following new bold-face warning to Accutane's physician package insert. FDA was still unaware of the new French warning. "WARNINGS—Psychiatric Disorders: Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events.

ADVERSE REACTIONS. In the post marketing period, a number of patients treated with Accutane have reported depression, psychosis and rarely, suicidal, ideation, suicide attempts and suicide. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy.

In its press release, Roche claimed that there was no proof of causation and that “teenagers are at particular risk for depression.”

The Spontaneous Reporting System database was reviewed for reports of depression, manic depression, manic reaction, depression psychotic, psychosis and suicide attempts.

In twenty cases of depression associated with isotretinoin, it was reported that depression resolved when isotretinoin was stopped and reoccurred when its use was resumed. The onset of depression occurred after a median of thirty-one days following the first course and after a median of thirty-five days following the second course of isotretinoin.

Of thirty-one suicide related reports considered to be relatively free of confounding factors, twelve described completed suicides and nineteen nonfatal reports described suicidal ideation or attempt. Completed suicides were reported primarily in males and non-fatal events mainly in females.

For the majority of patients with completed suicide, symptoms of depression prior to suicide were absent, while for the majority with non-fatal suicide events, a depressive syndrome had been noted prior to the event.

March 1998: England and Ireland required warnings of Accutane’s risk of psychiatric disorders which are similar to those in the U.S.

March 5, 1998: Just two weeks after Roche was compelled to strengthen warnings of Accutane’s risks of “depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide,” the FDA was forced to issue a warning letter requiring Roche to cease “false and misleading” advertisements which promote Accutane as an “effective treatment of severe acne . . . [that] minimizes negative psychosocial effects such as depression and poor self-image.” FDA added, “This claim is particularly troublesome in light of information recently presented in a Dear Doctor letter that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts and suicide.” The FDA charged Roche to “prominently disclose information about the psychiatric disorders described in the warnings section of the revised labeling” in Accutane advertisements.

A 3-23-98 FDA memo noted:

20 cases of challenge, dechallenge, re-challenge of depression on Accutane

Onset within medium 31d (9-100d) after 1st course, and 35 d (1-426d) after 2nd course Accutane

Recovery occurred within 1-8 d after stopping Accutane.

July 1998 the FDA became aware that French authorities had already required the addition of an Accutane “suicide attempt” warning in 1997, of the 1992–94 French study associating Accutane with depression, and of Roche’s failure to disclose this information to the agency.

On December 21, 1999, Roche prepared a “Psychiatric Disorder Issue Work-Up” for FDA, concluding, “Psychotic Disorders: There are a very small number (3) of reported cases that imply causality between a described psychotic disorder and Accutane administration . . . Suicidal behavior: There are no reports amongst the 168 reviewed that would imply causality between suicidal behavior and Accutane.”

On May 1, 2000: Roche changed the warnings on the prescribing information to include: “. . . depression, and rarely suicidal thoughts, suicide attempts and suicide . . . .” This is the first time that the actual packaging contained the full psychiatric warnings.

Accutane serious adverse events (1998-2000) were reviewed August 3, 2000. Statistics were derived from the FDA’s Adverse Event Reporting System (AERS): 2000: seven suicides; 1999: fifteen suicides; 1998: thirty-two suicides.

September 18–19, 2000: The FDA’s Dermatologic and Ophthalmic Drug Advisory Committee held a meeting on Accutane’s risks of birth defects and psychiatric disorders. FDA concluded that from 1982 to May, 2000, Accutane had been associated with 147 suicides and hospitalizations for depression. The Advisory Committee determined that further research was needed to establish Accutane’s risks of birth defects and of depression, suicide and other psychiatric disorders—but failed to specifically recommend that FDA require such studies. FDA suggested that such research should be conducted, but did not commit to requiring them. Yet, Roche claimed, “The number of suicides observed in the U.S. in the Accutane-exposed cohort is much less than would have been predicted... There is plainly no excess of observed suicides in the Accutane-exposed population (32) compared to what would be predicted in the age-matched general population.”

U.S. Representative Bart Stupak and seven members of Congress wrote to Patrick Zenner, President and CEO of Hoffman-LaRoche, on October 11, 2000 presenting specific recommendations Roche and FDA should take regarding Accutane.

There were over 500 formal adverse reaction reports of suicide, suicide attempt and suicide ideation recorded by national and international health agencies for Roaccutane/Accutane.

Accutane has the fourth highest record of adverse reaction reports in the U.S.

Over 500,000 prescription medications are sold in the U.S yearly.

On October 17,2000, Roche noted the following actions:

Roche will provide the FDA with a proposed Medication Guide (MedGuide) on Accutane before the end of the month. This document will include warnings of birth defects as well as a discussion of psychiatric events consistent with the professional label.

At the time, we will provide FDA with a revised informed consent form incorporating the psychiatric information in the current labeling.

As recognized by the FDA Advisory Committee, designing a scientifically sound approach to studying this matter raises complex methodological issues from both a scientific as well as social perspective. Roche is committed to working with FDA to design a feasible approach to study this issue and to fund that effort.

Roche noted on October 25, 2000 that it was developing a risk management program for Accutane. The program would detail plans for management of psychiatric adverse events and proposed drafts of the Medication Guide and Informed Consent.

On October 25, 2000, Roche noted that their risk management program included a medication guide for patients.

The patient should understand that there are some Accutane patients who have become depressed, had mood changes, and, in rare instances had suicidal thoughts, made suicide attempts or committed suicide. Some patients have had additional signs of anxiety and depression while taking Accutane. While it is not known if Accutane caused patients to behave this way, it is important that if you have a change in mood, sleep patterns, or irritability or have thoughts of suicide that you will immediately inform your prescriber of these changes.

The January 2001 "Medication Guide for Accutane" noted:

#2 Mental problems and suicide. Some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed serious mental problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking Accutane have had thoughts about hurting themselves or putting an end their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not take appear depressed. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane.

On January 9, 2001 the FDA wrote a letter to consumer and healthcare providers regarding inquiries about Accutane to the FDA, stating, "The risk of causing birth defects and psychiatric adverse events, including depression and suicide was brought before the Dermatologic and Ophthalmic Drugs Advisory Committee on September 18 and 19, 2000. Although, no clear casual link has been established, the Committee members concluded that further steps are necessary in addition to the warnings already in place by the manufacturer and the FDA to ensure the safe use of this drug."

As noted by Representative Bart Stupak to the FDA on March 1 and May 25, 2001, "A hand audit was requested of thirty-eight cases to make sure there was not any duplication. Many of these deaths occurred before October 2000, but these families did not realize that there was a connection between Accutane and their child's death until the airing of the Today Show."

As of January 2, 2001, seventy-two suicides had been reported. Of the list of thirty-eight names submitted on March 1, 2001, twenty-two are new cases.

On May 25, 2001, Representative Stupak noted to the FDA regarding independent scientific study.

The FDA's November 14, 2000 letter to Rep. Bart Stupak stated that the FDA had initiated discussions with the National Institute of Mental Health to address further research needs. The FDA would work with Hoffman-LaRoche as well as the National Institute of Mental Health on recommendations to help ensure that independent studies proposed be conducted in a scientifically valid manner.

Roche convened its panel of scientific experts to determine how a study should be conducted and that the FDA and National Institute of Mental Health would be allowed to comment and participate in the design of the research.

Eight members of Congress recommended that "Roche should commit to underwriting all necessary independent controlled studies on Accutane's risk of depression, suicidal ideation, suicide and other psychiatric disorders. Such studies should be designed in collaboration with the FDA and be conducted by independent investigators."

June 2002 Roche revised the package insert for Accutane to note that,

Possible serious side effects of taking Accutane include birth defects and mental disorders. Some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Symptoms of these problems include sad, "anxious" or empty mood, irritability, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on Accutane becoming aggressive or violent. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane.

## **20.8 OPDRA Study**

In 1998, FDA OPDRA analyzed spontaneous adverse drug event reports of positive dechallenge/rechallenge cases of depression, mania, psychosis, and suicide attempt. The 2998 case series supported the Accutane labeling change, which included a warning concerning psychiatric disorders. The warning stated that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts, and suicide.

There were twenty cases in this report. Nineteen were U.S. cases. There were fourteen cases of depression, five cases of psychosis, and one case of a mood disorder. The cases were evenly distributed between male and female. The median age was twenty years. Five cases had a psychiatric history, and five patients required hospitalization.

In summary, there were forty-one Accutane associated dechallenge/rechallenge cases. Seventy-six percent were without a reported psychiatric history. The median time to onset of symptoms during the first course of Accutane was thirty days, and a median recovery time of 4.5 days. During the second course, or the rechallenge course, the time to onset of symptoms was shorter in the cases that provided the information. Also, after the second course of Accutane, depression persisted in some patients after discontinuation of Accutane or medical intervention. There was a possible dose-response to Accutane observed in six patients.

In conclusion, dechallenge/rechallenge cases provide strong evidence to support a link between a drug and an observed adverse event. Forty-one cases of positive dechallenge/rechallenge which provide further evidence to support a relationship between Accutane and depressive symptoms.

## **20.9 FDA Postmarketing Study**

### **A. Dr. Wysowski (FDA, Postmarketing Experience Suicide and Depression)**

Today I'll be summarizing reports that FDA received of suicide and depression in patients treated with Accutane. Reports are from the United States only with Accutane as the suspect drug entered in the FDA's database from marketing in 1982 to May 2000.

Over the eighteen-year period of marketing, the FDA received reports of thirty-seven U.S. patients who committed suicide, twenty-four on Accutane and thirteen after stopping the drug.

Individuals who committed suicide were mostly male. The median age was seventeen. The median time on Accutane to suicide was about three months. For individuals who committed suicide after stopping the drug, the median time to suicide after stopping Accutane was 2.5 months.

Twenty-two percent of suicide cases were reported to have a psychiatric history. About 57 percent had other possible contributing factors for depression. These included personal relationship, problems, stressful life events, substance abuse, family history of psychiatric disorders, and others. Together, 62 percent were reported to have either a psychiatric history or possible contributing factors. About half of the reports, 49 percent, were received in 1998, after suicide and depression were added as a warning to the product labeling.

In addition to the suicides, the FDA received reports of 110 U.S. Accutane users hospitalized for depression, suicidal ideation, and suicide attempt, eighty-five on Accutane and twenty-five after stopping the drug.

Individuals hospitalized for depression were more likely to be female. The median age was seventeen. The median time on Accutane to hospitalization was about one month. For those hospitalized after stopping the drug, the median time to hospitalization after stopping Accutane was three months. Forty-four percent were reported to have a psychiatric history. Fifty-two percent had other possible contributing factors for depression, and together 69 percent had either a psychiatric history or possible contributing factors. Forty-one percent of reports were received in 1998, the year depression and suicide were added to the labeling. And the median peak dose was 1.1 milligram per kilogram of body weight per day.

About a third of patients had positive dechallenges with psychiatric treatment, and nearly a third experienced persistent depression after drug discontinuation. One person had a positive rechallenge, while three others were rechallenged and were able to continue on Accutane with alcohol abstinence, dose lowering, and continued use of an antidepressant.

As of May 2000, the FDA received reports of 284 U.S. Accutane users with non-hospitalized depression. Forty-five percent were received in 1998 after depression and suicide were added as a warning to the labeling. About half of the non-hospitalized patients reported accompanying side effects such as dry mucous membranes, headaches, hair loss, and joint and muscle pain. About 50 percent of reports were from consumers and relatives, a higher proportion compared with most reports for most drugs.

The top ten adverse events reported for Accutane include depression that ranks number 6. Of course, the degree of under-reporting is unknown and may be quite substantial.

There are several pieces of evidence supportive of a possible association between Accutane and depression and suicide. These include the relatively large number of reports of serious depression, more than for most drugs in the FDA's database, the temporal association between use of Accutane and onset of depression, positive dechallenges in individuals who felt better once Accutane was discontinued and psychiatric care was obtained, and positive rechallenges in individuals who experienced symptoms again after restarting the drug.

Also, some individuals had no reported psychiatric history or possible contributing factors, and there are similar case reports of depression and suicide in Accutane users in the medical literature.

However, there are several complicating factors. Some individuals had previous courses of Accutane without depression. There are high rates of depression and suicide in the teen years, making the independent contribution of Accutane with depression difficult to assess. And many cases had a psychiatric history and other factors, including acne itself, that could have predisposed them to depression. Also, most serious cases did not improve with Accutane discontinuation alone. Psychiatric intervention was frequently required.

Last, a large retrospective cohort epidemiological study, referred to as the Jick study for the principal investigator, Susan Jick, that was funded by Hoffmann-LaRoche, found no increased risk of depression in individuals prescribed Accutane compared with those prescribed antibiotics for acne. However, the study had some important limitations.

Patients were not interviewed, so depression was under-diagnosed and under-ascertained. The study did find an increased relative risk of 2 for suicide attempts and suicides in patients prescribed Accutane. The relative risk had wide confidence intervals of 0.4 to 10, and was not statistically significant. It's possible that a larger sample size could have resulted in a statistically significant relative risk with Accutane.

So, in summary, the FDA has received reports of suicide and serious depression in U.S. Accutane-treated patients. The case reports are suggestive of an association with Accutane, but do not allow definitive determination as to whether Accutane causes depression and suicide in treated patients.

## **B. Dr. O'Connell (FDA, Biological Plausibility and Risk Management) 120**

If you look in the published cases about time to offset, the most useful data—actually the paper has already been referred to I think by Dr. Byrne and perhaps by the sponsor as well that was published by Scheinman et al. in 1990. I want to emphasize that this was not a trial done to examine the psychiatric adverse events of Accutane. This was just 700 patients—I believe it was an NIH trial that had received Accutane for various indications. It wasn't even all acne. Seven patients in that group had enough psychiatric problems to come to attention. Let's put it that way. But of those seven patients that they reported in this paper, it's notable that the symptoms in all seven of them resolved within one week of stopping Accutane, and one of the patients was rechallenged and did have a positive rechallenge.

There's another paper published by Hazen et al. in 1983, earlier. Again, this was not a trial to study this. This was just six patients who presented with enough symptoms to come to attention out of 110 patients. This paper doesn't actually state the exact time. It just notes that of these six patients, five continued the drug despite the depression, but that when the treatment course was over, their symptoms rapidly resolved upon discontinuation.

The other thing I want to point out is that the psychiatric adverse events that are reported with Accutane aren't occurring in isolation. There are other adverse events that occur with Accutane, as with all drugs. If you look at the organ system categories that adverse events are categorized into, there are twenty-eight of them I believe. For Accutane, the central nervous system, interestingly, ranks second only to psychiatric in the highest percentage of serious adverse events—serious adverse events—in the Hoffmann-LaRoche postmarketing database for Accutane. So, I think it's clear that Accutane affects the central nervous system.

The bottom line here is that none of these elements that anyone has described this morning or that I'm describing right now—none of these elements of adverse event assessment nor their totality proves—proves—in a rigorous sense that Accutane causes psychiatric disease. But we're very concerned about the data that's been presented this

morning.

This is another paper that Dr. Byrne already referred to. I think this was three cases that actually Dr. Bravard and his colleagues reported in 1993. In the last sentence in his paper, he advised us to be vigilant. So, that's really why we're here today. We want to explore what we need to do to be vigilant. What's appropriate, what's feasible given the information that we have and how might we go about resolving the uncertainty.

Another practical question. Is there an identifiable subset of patients at increased risk? Then we don't have to apply risk management to everybody. We just apply it to the people who need it. Another question that I think people out there actually using this drug would very much like to know is, if symptoms do occur in this setting, is a dose adjustment or addition of treatment with antidepressants safe, or do you really have to discontinue the Accutane, which obviously has consequences for the patients who have severe acne that can lead to scarring if they don't get effective treatment?

### **C. Dr. Branch**

I come in with a slight tone of dissent. I'm a strong proponent of evidence based medicine. I think that it's extremely difficult to see the signal in the background of the psychiatric illness here. I think the most convincing data is the dechallenge/challenge data that the FDA presented. Having sort of seen the quality or heard about the quality of the various data sources, it seems to me it is likely that there is a small but real temporally related side effect profile in a minority of subjects.

I like the idea of doing future studies that look at the potential for pharmacogenetics to identify predisposed people, but we don't have the science to back that yet.

I'm concerned that were going to be taking what is a therapeutic opportunity to link dermatologists and psychiatrists to mandate something that may not be as simple as that. So, my concern is that the patients are given a current state of knowledge in all its imprecise natures. I am concerned that there is a rush to condemn when we don't actually have the requisite information. I think the future studies could be designed and could really throw light onto both mechanisms, identifying potential people at risk, and being able to come up with strategies of what to do if you see something, but I think we need to be very careful that we tell people what we know and not what we feel.

## **20.10 Selected Abstracts from Accutane 2002 Prescribing Information**

### **A. Indications and usage**

Severe recalcitrant nodular acne: Accutane is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, for female patients of childbearing potential, Accutane is indicated only for those females who are not.

### **B. Warnings**

#### **1. Psychiatric disorders**

Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events.

#### **2. Pseudotumor cerebri**

Accutane use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue Accutane immediately and be referred to a neurologist for further diagnosis and care.

#### **3. Hearing impairment**

Impaired hearing has been reported in patients taking Accutane; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this event have not been established. Patients who experience tinnitus or hearing impairment should discontinue Accutane treatment and be referred to specialized care for further evaluation.

#### 4. Vision impairment

Visual problems should be carefully monitored. All Accutane patients experiencing visual difficulties should discontinue Accutane treatment and have an ophthalmological examination.

### C. Adverse reactions: Clinical trials and postmarketing surveillance

The adverse reactions listed below reflect the experience from investigational studies of Accutane, and the postmarketing experience. The relationship of some of these events to Accutane therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving Accutane are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, e.g., of the lips, nasal passage, and eyes).

**Body as a whole:** allergic reactions, including vasculitis, systemic hypersensitivity (see PRECAUTIONS: Hypersensitivity), edema, fatigue, lymphadenopathy, weight loss.

**Musculoskeletal:** skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, mild to moderate musculoskeletal symptoms including arthralgia, transient pain in the chest, elevations of CPK, arthritis, tendonitis, other types of bone abnormalities

**Neurological:** pseudotumor cerebri, dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures, stroke, syncope, weakness

**Psychiatric:** suicidal ideation, suicide attempts, suicide, depression, psychosis, emotional instability. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy.

**Special senses:** Hearing: hearing impairment (see WARNINGS: Hearing Impairment), tinnitus. Vision: corneal opacities (see WARNINGS: Corneal Opacities), decreased night vision which may persist (see WARNINGS: Decreased Night Vision), cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances

## 20.11 Selections from Accutane Informed Consent/Patient Agreement

4. I understand that some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane. Some people have had other signs of depression while taking Accutane (see #7 below).

Initials: \_\_\_\_\_

7. Once I start taking Accutane, I agree to stop using Accutane and tell my provider right away if any of the following happen. I:

- start to feel sad or have crying spells
- lose interest in my usual activities
- have changes in my normal sleep patterns
- become more irritable than usual
- lose my appetite
- become unusually tired
- have trouble concentrating
- withdraw from family and friends
- start having thoughts about hurting yourself/myself or taking your/my own life (suicidal thoughts)

Initials: \_\_\_\_\_

8. I agree to return to see my provider every month I take Accutane to get a new prescription for Accutane, to check my progress, and to check for signs of side effects.

## 20.12 Medication Guide: Accutane Capsules

2. Mental problems and suicide. Some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane.

All patients should read the section in this Medication Guide “What are the signs of mental problems?”

For other possible serious side effects of Accutane, see “What are the possible side effects of Accutane?” in this Medication Guide.

All patients should read the rest of this Medication Guide.

What are the signs of mental problems?

Tell your provider if, to the best of your knowledge, you or someone in your family has ever had any mental illness, including depression, suicidal behavior, or psychosis. Psychosis means a loss of contact with reality, such as hearing voices or seeing things that are not there. Also, tell your provider if you take medicines for any of these problems.

Stop using Accutane and tell your provider right away if you:

- start to feel sad or have crying spells
  - lose interest in your usual activities
  - have changes in your normal sleep patterns
  - become more irritable than usual
  - lose your appetite
  - become unusually tired
  - have trouble concentrating
  - withdraw from family and friends
  - start having thoughts about hurting yourself/myself or taking your/my own life (suicidal thoughts)
- Serious mental health problems. See “What is the most important information I should know about Accutane?”
- Serious brain problems. Accutane can increase the pressure in your brain. This can lead to permanent loss of sight, or in rare cases, death. Stop taking Accutane and call your provider right away if you get any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients taking Accutane have had seizures (convulsions) or stroke.

Four cases of neuropsychiatric adverse effects from Accutane are presented in section 20.18. There is need for improvement on the part of the manufacturer to improve the quality of specific information presented to patients and to prescribers. Because of the potential seriousness of neuropsychiatric effects, a comparable effort to that given to birth defects, must be expended.

## 20.13 Adverse Drug-Reaction Reports

Among the many anti-acne products available, the five most commonly prescribed treatments are Dianette, doxycycline, minocycline, oxytetracycline, and tetracycline. Based on available information, there are more reports of psychiatric adverse events and suicide worldwide from isotretinoin than from the use of the other five acne therapies combined. Table 20.1 shows the worldwide reports of psychiatric events attributable to the six anti-acne medications. Of these 1,830 psychiatric events, isotretinoin was implicated in 59.8 percent (1,095/1,830). Second to this was minocycline, implicated in 14.2 percent (261/1,830). Forty-seven and fifty-six cases of suicide and suicidal ideation were reported in association with the use of Accutane, respectively, with none being reported for the other medications. Of seventy-five cases of attempted suicide reported, 89.3 percent (sixty-seven out of seventy-five) were associated with the use of isotretinoin, with 4 percent (three out of seventy-five) associated with the use of both Dianette and tetracycline, and 2.6 percent (two out of seventy-five) for minocycline. ADR data for the U.K., as shown in Table 20.2, reflects a similar pattern, with 51.9 percent (135/262) of psychiatric ADRs attributed to isotretinoin. In addition, all cases of suicide/suicide attempt/suicidal ideation were associated with the use of this medication. The source for this data relies on voluntary reporting and probably represents significant underreporting, as not all serious ADRs are reported.

Table 20.3 shows the number of prescription items dispensed in England from 1982 to 1997. Isotretinoin, while attracting the largest percentage of psychiatric ADRs, had the lowest number of prescriptions issued (12,400). During this period 1,214,600 prescriptions were dispensed for Dianette, of which the indication for 184,200 prescriptions was acne. Dianette was implicated in only 1.9 percent (five out of 262) of psychiatric ADRs.

Minocycline is used extensively in the treatment of acne vulgaris (8,802,000 prescriptions issued between 1982–1997.) Between 1970–1997, 6.5 million patients were treated with minocycline in the U.K.<sup>39</sup> A total of forty-five psychiatric adverse events were received by the MCA between 1973 and 1997. Accutane has a U.K. patient exposure of 50,000 (eight million worldwide, PharmFocus data) and has received reports of 135 psychiatric adverse events. Based on these figures, the incidence rates of psychiatric adverse reactions for Accutane and Minocycline are 270 and 0.692 per 100,000 people treated, respectively. These medications (with the exception of Accutane) are used to treat conditions other than acne. As patient exposure data for these medications, where the indication was acne, was unobtainable the frequency of psychiatric reactions attributable to these medications, in the population of acne patients, remains unknown.

## 20.14 Submission of ADR Reports

ADR reports often paint an incomplete picture, as the cases filed each year represent only a fraction of actual cases. According to the U.K.'s MCA, only 10–15 percent of serious ADRs are ever reported.

Under regulations, a pharmaceutical company must submit all ADR reports to the FDA within twenty-one days of receipt. The FDA, on January 5, 1998, sent a warning letter to Hoffman-LaRoche (New Jersey) for failing to submit a number of adverse drug-experience reports that were both serious and unexpected, within fifteen working days—as required by regulations (21 C.F.R. 314.80 (c)(1))—as recently as October, 1997, with some dating back to 1989.<sup>40</sup> The letter documented, among others, two ADR reports for Accutane which were received by the manufacturers on September 4, 1991 and July 24, 1991. The FDA received neither report until October 8, 1997 (FDA, personal communication). In one case, for Tigason, the company reported the adverse drug event almost eleven years after receiving the information.

## 20.15 Revised Label Warning

On February 25, 1998, the FDA issued a talk paper declaring new safety information regarding isotretinoin, as a result of adverse-event reports the agency received. The revised information leaflet now reads

Psychiatric disorders: Accutane may cause depression, psychosis and, rarely, suicide ideation, suicide attempt and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary . . . Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy.

Earlier information leaflets read, “depression has been reported in some patients on Accutane therapy. In some of these patients, this has subsided with discontinuation of therapy and recurred with reinstatement of therapy.”

Almost one year before this revision, the French product label was altered on March 3, 1997, to include “suicide attempt” as a side effect of isotretinoin therapy, and reads, “In rare occasions, neuropsychological problems have been recorded (behavioral difficulties, depression, convulsions and suicide attempts)” (French Product License, 1997). This revision was introduced in France following a prospective national inquiry (1993–1994), in which Roche and more than 2,000 state dermatologists participated. This inquiry followed a paper presentation, which reported on a suicide associated with isotretinoin therapy.<sup>35</sup> The results of this inquiry were presented at the Third Forum of the National and Provincial Journal of Dermatology at Mont Pellier (March 14–17, 1996) but were never published. It was almost one year later, before this warning was introduced in any other country. According to the *Star-Ledger* (November 16, 1998) “Roche never informed the FDA of this new label change, who did not learn of the French label warning until this summer [1998].” Revised warnings have now been introduced in Ireland (May, 1998) and the U.K. (April, 1998).

## 20.16 Defense of Accutane

In relation to the number of reports of depression and suicide associated with Accutane therapy, Roche denied the possibility of an association between isotretinoin and depression. When asked of this possibility Roche told the *Star Ledger* (November 16, 1998), “acne itself can be a risk factor for depression and it is well known that teenagers and young adults are at increased risk of depression/suicide.” Until recently, Roche attempted to capitalize on the belief that treating acne with Accutane may relieve depression, by placing journal advertisements, stating that Accutane was safe and effective in the treatment of what Roche describes as the “psychosocial trauma” and “emotional suffering” associated with acne. On March 5, 1998, the FDA issued a warning letter to Roche stating that the ads were “false or misleading and

promote Accutane for an unapproved use in violation of the Federal Food, Drug and Cosmetic Act, 21 USC 355(a), 352(a), 352(f), 331(a) and 331(d),” and Roche must immediately cease dissemination of same. The company claimed they had clinical support for their claims. One such study, by Rubinow,<sup>41</sup> showed a reduction in anxiety and depression in cystic acne patients receiving oral isotretinoin. However, this is not surprising, as any successful treatment—especially one of a severe cosmetic disorder, such as cystic acne—should relieve or reduce anxiety. The observed reduction in anxiety and depression was most significant in patients showing the greatest dermatological improvement. The FDA responded by stating that this study did not systemically examine the ability of Accutane to modify or prevent depression. Cotterill<sup>42</sup> has suggested that dermatological patients are at greater risk of suicide, and suggests early use of isotretinoin to reduce this risk. However, their findings are open to an alternative interpretation. All but one of the cases they described had long-standing psychiatric illness (manic depression, alcoholism) or other risk factors for psychiatric morbidity (e.g., recently bereaved) before being seen by the authors of the study.

## 20.17 Lawsuits

A number of lawsuits have been filed against Roche in connection with Accutane and its depressive side effects. In *Durham v. Hoffman-LaRoche*<sup>43</sup> a confidential settlement was agreed upon for the family of a man (currently age twenty-two) who suffers from severe depression caused by Accutane. The plaintiffs alleged that the manufacturers gave the medical community inadequate warning that the drug could cause severe psychiatric injury. The parties settled ten days before the scheduled trial date. The district court had previously ordered the manufacturer to produce about 100 ADR reports of depression in patients on Accutane in the past nine years, including the names of the reporting physician.

In *Talarico v. Roche* (Cook County),<sup>44</sup> which is still in progress, the plaintiff exhibited aggressive and violent behavior and mood changes after taking Accutane treatment.

## 20.18 Case Reports

### A. Jones/106079, filed August 8, 1997<sup>45</sup>

The defendant dermatologist prescribed Accutane for the treatment of plaintiff’s acne. The plaintiff developed depression immediately and subsequently developed psychotic depression, requiring hospitalization. The plaintiff alleges that the manufacturer and defendant failed to warn of the potential side-effects.

### B. Owensby, filed March 10, 1998<sup>46</sup>

The plaintiff, with no prior history of depression or psychological injury, became depressed after a third course of Accutane treatment for acne. The plaintiff subsequently committed suicide.

### C. Balsham, filed March 10, 1998<sup>47</sup>

The plaintiff was treated with Accutane for acne on three occasions between 1996 and 1997. Each treatment was approximately three months in duration. After the first treatment, she suffered depression and, subsequently, made two suicide attempts. She is currently under the care of a psychiatrist.

### D. Kenny Spaeth, filed June 30, 1998<sup>48</sup>

The plaintiff was prescribed Accutane and subsequently committed suicide.

Roche is now facing landmark legal action in association with Accutane. In the U.K., at least ten people have been granted legal aid to sue the manufacturer. This is the first step in a legal battle, which, if successful, could open the floodgates to thousands of compensation claims from people who have suffered marked personality changes, depressive conditions, and suicide attempts after taking the drug. U.K. solicitors believe compensation claims can be filed against Roche Products under the Consumer Protection Act of 1988, which makes manufacturers liable for faulty products, whether or not they are negligent.

## 20.19 Retinoids Implicated in Schizophrenia

Goodman has recently proposed retinoid dysregulation as a possible cause of schizophrenia.<sup>49</sup> Schizophrenia is now considered to be a neurodevelopmental disorder, with the first evidence of the disorder occurring in the midgestational period—the time when fetal brain is actively developing. Vitamin A, which is essential in gene regulation and expression, is particularly active in brain neurodevelopment at this time. Goodman has put forward three lines of evidence for an association. The first is the resemblance of symptom presentations of retinoid toxicity to the stigmata of schizophrenia, such as thought disorder, mental deficit, enlarged ventricles, microcephaly, and congenital malformations. The second line of evidence comes from the finding that specific gene loci, which have been suggestively linked to schizophrenia, are

known loci of genes within the retinoid-signaling system. Retinoids are handled in the body by a complex genetic cascade necessary for the metabolism of retinol to retinoic acids. The major genes in the retinoid cascade are the nuclear retinoid receptors RAR and RXR. The loci of two of the genes involved in the regulation of this cascade, RXRa and RARa, have been suggestively linked to schizophrenia. It has recently been found that RXR is necessary for the expression of dopaminergic neurons in the midbrain region in mice, which have been implicated by numerous studies as abnormal in schizophrenia.<sup>50</sup> The third line of evidence shows schizophrenia genes as targets of retinoid regulation. Retinoic acid binds to RARs and RXRs, and this complex then binds to specific regions of the target genes. In this way, it regulates the expression of multiple target genes. Among the many genes shown to be targets of retinoic acid are dopamine and serotonin, both of which have been proposed as candidate schizophrenia genes.

Alteration of neurotransmitters is a classic hallmark of the psychoses. Recent work has shown that retinoic acid is a major regulator of several of the genes involved in neurotransmission.<sup>51</sup>

## 20.20 Teratogenesis of the Retinoids

It was recognized in the 1930s that maternal insufficiency of vitamin A during pregnancy resulted in fetal death and severe congenital malformations. It was subsequently discovered in the early 1950s that embryonic malformations also occur in the presence of excessive amounts of vitamin A.<sup>52</sup> Vitamin A has since been well documented as a teratogen in animals<sup>53</sup> and in humans.<sup>54–56</sup> Major target tissues include the heart, skull, skeleton, limbs, CNS, brain, eyes, and congenital malformations. Teratogenicity in humans of doses above 10,000 IU/d of preformed vitamin A as retinyl esters and retinol has been reported.<sup>57</sup> It has been suggested that among the infants born to women who take more than 10,000 IU of preformed vitamin A in the form of supplements, about one in fifty-seven is born with a birth defect attributable to the high vitamin A intake of the mother.<sup>58</sup> The U.S. National Research Council currently suggests an RDA for male adults of 1000 µg RE (3330 IU of vitamin A) and 800 µg RE (2670 IU) for women.

Several animal studies subsequently demonstrated the teratogenic affect of retinoids,<sup>59–62</sup> which are associated with ocular, thymus, and craniofacial abnormalities; ear defects; cleft palate; circulatory disorders; and urogenital malformations;<sup>63</sup> as shown in Table 20.4. Defects of the CNS include anencephaly, microcephaly, meningocele, and spina bifida. Retinoids act directly on the nucleus, binding to receptors that selectively regulate transcription of a number of genes. They are part of a complex interaction with growth factors, steroids, and oncogenes, in regulating gene expression.<sup>64</sup> Small changes in retinoid levels can produce changes within multiple systems in the cell. Retinoid levels in mammals are normally tightly controlled by a series of transport, binding, and receptor proteins—the synthesis of which are highly regulated. Early in embryogenesis, the ability to synthesize these proteins has not yet developed and a relatively unrestricted transfer across the placenta can take place, perhaps explaining the high teratogenicity of orally administered retinoids. If isotretinoin exposure occurs within the first trimester at the first level, death can occur via abortion or stillbirth. This occurs in about 40 percent of cases. Of those infants who are born, 25–30 percent are malformed.

## 20.21 Isotretinoin: When Warnings are Not Enough

Isotretinoin is the most potent teratogen on the market. Its teratologic potential exceeds even that of thalidomide. First marketed in September of 1982 for the treatment of severe, recalcitrant cystic acne, FDA classified isotretinoin as Category X—contraindicated for use during pregnancy. It was a recognized animal teratogen, and a statement to that effect was included in the package insert. Within six months of its release, reports of birth defects associated with first-trimester exposure to this drug were reported to the New Jersey Birth Defects Registry.<sup>65</sup> Later in 1983, case reports and case series describing the range of birth defects associated with this drug began to emerge. By August 15, 1983, twelve cases of adverse pregnancy outcomes associated with isotretinoin exposure were reported to the FDA.<sup>66</sup> In one prospective follow-up study, eight of thirty-six pregnancies exposed to isotretinoin resulted in spontaneous abortion during the first trimester; four resulted in live-born infants with at least one major malformation; one, in a malformed stillborn infant; and twenty-three, in infants without malformations.<sup>67</sup> This study found a relative risk of 25.6 for the defects associated with isotretinoin embryopathy.

## 20.22 Dermatological Advisory Committee

The official package labeling in effect from December 1, 1982, through August 15, 1983, indicated that the product was a potential human teratogen. It advised the use of effective contraceptive methods and that women be fully counseled on the potential risk to a fetus, should they become pregnant while undergoing Accutane treatment. Following petitions from the Health Research Group to the FDA, Roche, in 1984, added to the label a recommendation that a pregnancy test should be performed. The labeling also reflected the 1983 reports of birth defects associated with first trimester exposure

to Accutane.

On April 22, 1988, the *New York Times* reported that “Officials of the Food and Drug Administration estimated that from 900-1,300 babies were born with ‘severe birth defects’ because of the drug from 1982 to 1986,”<sup>68</sup> but Hoffman-LaRoche challenged these figures. Four days later, at the FDA’s Dermatology Advisory Committee meeting, the FDA revealed that a total of sixty-two birth defects attributed to Accutane had been recorded by the FDA to date. These findings were presented to FDA’s Dermatologic Drugs Advisory Committee in 1988, requesting its removal from the market. Officials of the American Academy of Pediatrics called for a ban on the drug—unless a foolproof method could be devised to prevent pregnancies among users—while dermatologists argued vigorously to keep the drug on the market.

The outcome of the agency meeting, proposed by Philip Del Vecchio, director of Drug Regulatory Affairs at Hoffman-LaRoche, was to toughen the warnings about the risk of birth defects and a recommendation that the drug was not to be used by a woman of child-bearing age unless the following criteria were met:

- Patient has severe, disfiguring, recalcitrant acne.
- The patient is reliable in understanding and carrying out instructions.
- The patient is capable of complying with the mandatory contraceptive measures.
- The patient has received both oral and written warning of the hazards of pregnancy and has indicated her understanding and acceptance of those warnings in writing.
- Pregnancy has been definitely excluded through a negative serum pregnancy test and appropriate history and physical examination.
- The patient will begin therapy only on the second or third day of the next normal menstrual period.

### 20.23 The FDA’s Battle with Accutane

During the 1980s and early 1990s, FDA officials debated options to control and prevent the occurrence of Accutane-exposed pregnancies—including its removal from the market. The *Columbus Dispatch* (July 14, 1996) documented David Grahams’ (section chief of the FDA’s epidemiology branch) investigation of the situation and detailed several documents and memos which showed the FDA battling itself and Hoffman-LaRoche. Such documents revealed that between 1982 and 1987, approximately 1.2 million people were treated with Accutane. Five hundred sixty thousand were women, of which 427,000 were between the ages of twelve and forty-four, and more than 90 percent of females treated did not have severe, cystic acne. In a 1990 memo Graham wrote, “The magnitude of injury and death has been great and permanent with 11,000 to 13,000 Accutane-related abortions and 900-1,100 Accutane-related birth defects. There is no alternative to immediate withdrawal.”

An Accutane monitoring group, consisting of four FDA physicians, said Hoffman-LaRoche was biased in its own studies into birth defects, according to the newspaper, and “the company, as well as some physicians, urged women who got pregnant while using Accutane, to get abortions.”

### 20.24 RTE-PrimeTime

On November 11, 1998, RTE’s (Irish Television) *Prime Time* delivered a documentary on Roaccutane. The program entitled, “Roaccutane: Cover-Up,” was researched by Cathy Moore. The program exposed internal documents obtained showing how Roche’s own scientists were warning the company of the likelihood of birth defects prior to marketing. One such document by Dr. Jerome Kahm (Roche) read, “I think that the potential teratogenicity of the retinoids should be given serious consideration. It would be prudent to alert a sexually active female being treated with a retinoid, in the strongest possible terms, of the potential of conceiving a deformed child. There is no way, in good conscience, to avoid this issue. The animal data, I think, can be extrapolated in terms of a potential danger. The potential of teratogenesis cannot be ignored.”

The program revealed how, in clinical trials before the drug was approved, Roche required women to provide a negative pregnancy test before taking the drug. Despite these efforts, at least five women became pregnant. Roche offered to pay for the abortions. Three opted for abortions, while two had late miscarriages. When FDA sanctioned Accutane, however, it did not stipulate that Roche include a warning on the product label that a pregnancy test be performed prior to therapy.

A survey of the basic science literature suggests that this now well-established risk should not have come as a surprise to clinicians. Seven studies in lab animals were published in the five years before isotretinoin’s release,<sup>69-75</sup> suggesting an association between retinoic acid and fetal malformations. The characteristic cardiac and craniofacial abnormalities subsequently observed in humans, were described in a 1980 study of hamsters.<sup>69</sup>

## 20.25 Inadequate Testing

It was well known prior to market release in 1982 that isotretinoin was teratogenic in animals. Roche's own preclinical animal experiments demonstrated this. However, the company conducted no developmental neurotoxicity testing, because it was not required to do so by the FDA. In 1985, Lammer<sup>67</sup> demonstrated unequivocally a human malformation syndrome caused by isotretinoin, based on a study of all the known retrospectively ascertained cases of isotretinoin-associated malformations (cardiac, thymic, craniofacial, and CNS). Vorhees<sup>76</sup> believed that even without this data, the company could have predicted that isotretinoin would also be a development toxin. Animals exposed to retinoids during organogenesis exhibit a variety of dysfunctions in the absence of malformations. Based on this data, he predicted that "isotretinoin-exposed children would be mentally retarded and learning disabled and further, that such effects would be seen not only in those malformed, but also in those who were otherwise normal in appearance."<sup>77</sup> Regrettably, this was proven by Adams and Lammer in 1991, in a human prospective study.<sup>78</sup>

## 20.26 Prescribing Patterns: Failure to Comply

Hoffman-LaRoche implemented its Pregnancy Prevention Program for Women on Accutane in late 1988, although it was not fully implemented until mid-1989.

New guidelines put a substantial burden on the dispensing physician. The rules were time-consuming, and required careful monitoring of patients who may be unaccustomed to adhering strictly to medical directions. There are also the natural limits to their effectiveness. Even if guidelines are strictly adhered to, pregnancy will occur at the rate of contraceptive failure. There is no easy way to identify physicians who do not comply and force them to do so.

A survey of 670 U.S. dermatologists in 1992 supported the prediction of less than 100-percent compliance—even by trained physicians—prescribing Accutane. Forty-five percent of dermatologists were not limiting prescribing to those with cystic acne. Signed, written informed consent was obtained by only 59.1 percent of respondents.<sup>79</sup> Labeling guidelines state that the drug is contraindicated, unless the patient "has received both oral and written warning of the hazards of taking Accutane during pregnancy." Only 73.5 percent of physicians performed a pregnancy test, and only 36.3 percent performed follow-up pregnancy tests during therapy. A prescriber who fails to heed labeling guidelines—especially the strong warnings about pregnancy while taking Accutane—would almost certainly be found negligent in performing the prescribing function.

An analysis of a survey among pharmacovigilance structures conducted in France from 1987 to 1995 was assessed, due to an exposition to isotretinoin and an prospective inquiry concerning isotretinoin prescription in women conducted among pharmacists.<sup>80</sup> Three hundred eighteen pregnancies were examined. Thirty-three percent of these pregnancies began during the month after isotretinoin withdrawal, 51 percent during treatment, and 16 percent before treatment. Of the women with pregnancies conceived during treatment and one month after treatment, contraception was not prescribed in 15 percent. Of the 173 women who were interviewed in pharmacies, only 14 percent had received full information about isotretinoin and pregnancy. In April of 1997, two changes were made to the French prescribing regulations:

- Women must have a negative pregnancy test before receiving the product. Subsequent tests must be conducted every two months during treatment. Negative pregnancy-test results must also be shown to the dispensing pharmacist.
- At the end of treatment, any remaining capsules must be returned to the pharmacy. Women of childbearing age must continue contraception for a month and take another pregnancy test five weeks after treatment ends.

Three hundred eighteen pregnancies had been reported in French women taking Accutane over the ten years from 1986 to 1996—an incidence of 0.6 per 1,000 women treated. Eighty percent of these pregnancies were terminated.<sup>40</sup>

Other surveys confirm less strict compliance with pregnancy tests and signed consent before initiation of treatment, with 4 percent of dermatologists in the Netherlands<sup>81</sup> and 80 percent in Australia<sup>82</sup> undertaking pregnancy tests. Use of oral retinoids for other than the specified indications has been reported<sup>79,81</sup> as well as prescription by unauthorized doctors,<sup>83</sup> and use of drugs left over from previous prescriptions or obtained from friends or relatives.<sup>84</sup>

## 20.27 License Indications: Failure to Comply

The license indication for Accutane states, "Accutane is indicated for the treatment of severe recalcitrant nodular acne . . . Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy including systemic antibiotics."

Despite the plethora of serious side effects associated with Accutane therapy and the high number of exposed pregnancies that occur every year due to poor compliance with prescription guidelines, there is evidence of prescriptions

written outside of the specified indication. Between 1983 and 1986, severe acne was the main indication for isotretinoin (79 percent of patients) at the General Infirmary at Leeds, U.K., with only 21 percent of treated patients graded as having moderate acne. This contrasts with current figures of 74 percent of patients with mild or moderate acne and 16 percent only with severe acne.<sup>85</sup> In the U.K. and Italy, such patients represented the greatest number of patients so treated (In the U.K., 74–76 percent, and 50 percent in Italy).<sup>2</sup> Layton claims that long-term studies have demonstrated that isotretinoin has an excellent safety and efficiency profile, irrespective of the severity of the complaint.<sup>86</sup> At a consensus meeting in Brussels, twelve dermatologists suggested that perhaps it was now appropriate to consider extending the license indications for Accutane to include these “other groups of patients,” that is, those with mild or moderate acne.<sup>87</sup>

Cunliffe has clearly put forward his definition of the acne population who require oral isotretinoin therapy and they include, “patients with mild or severe acne” and “those with mild acne who are very depressed or for whom employment is difficult.”<sup>88</sup> This type of promotion appears to present to patients an unrealistically high expectation of what life will hold after successful treatment of their acne—i.e., a great job or an improved social life. Cunliffe believes “patients with acne-induced psychological distress such as severe depression or dysmorphophobia should be treated with isotretinoin, even when such patients display apparently mild acne, and patients who show only partial response to antibiotics should be prescribed isotretinoin in order to minimize psychological disturbance, independently of the severity of the acne.”<sup>85</sup>

## 20.28 Etretinate and Acitretin

In 1974, second-generation retinoids with an aromatic ring began to emerge. Etretinate (Ro 109359) (Tigason) and acitretin (Ro 10-1670) (Soriatane) were among this group, first demonstrating their effectiveness in the treatment of severe psoriasis in 1975 and 1984, respectively. In June of 1997, acitretin was approved by the FDA as a replacement for etretinate for similar indications.

### A. Metabolism

Acitretin is the major metabolite of etretinate. Both are very similar in chemical structure (etretinate is the ethyl ester of acitretin), but differ significantly in their physicochemical properties. Etretinate is an uncharged molecule. It is highly lipophilic (fifty times more so than acitretin) and so is sequestered into adipose tissue, where it is released slowly, resulting in a long-elimination half-life of more than 100 days. In contrast, acitretin is negatively charged, does not accumulate in adipose tissue, and therefore is eliminated from the body more rapidly (T<sub>1/2</sub> is approximately two days). After absorption, etretinate is predominantly bound to lipoprotein, while acitretin binds albumin. Both appear to be eliminated exclusively by metabolism, with the resultant metabolites excreted via bile and urine.

### B. Therapeutic use

Both drugs have proven their excellence in the treatment of chronic-plaque psoriasis. However, the most common form, plaque-type psoriasis, responds irregularly to both.<sup>89</sup> Complete remission usually requires an additional treatment such as topical corticosteroids, dithanol, or PUVA or UVB phototherapies. Best results occur in the treatment of palmoplantar type pustular psoriasis, where they are considered first-choice treatments.<sup>90</sup> They both show very good efficacy in various keratinization disorders and in ichthyosis. Severe forms of Darier’s disease are good indications, where the aromatic retinoids give better results than any other treatment.<sup>91</sup>

Both have indications in premalignant skin lesions, such as human papillomavirus-induced tumors<sup>92,93</sup> and actinic keratoses.<sup>94</sup> In the basal-cell carcinoma syndrome and in xeroderma pigmentosum, these drugs are able to dramatically reduce the incidence of malignant degeneration of skin lesions.<sup>95</sup>

### C. Toxicities and adverse reactions

Although both acitretin and etretinate are effective therapies, their use is associated with significant toxicities. The side-effect profile of both drugs qualitatively resembles that of vitamin A or hypervitaminosis A. The most frequently reported skin and mucous-membrane effects include cheilitis, dry mouth, blepharoconjunctivitis, xerosis of the skin, alopecia, and paronychia. Systemic toxic effects also occur. Abnormal elevations in serum transaminases have been reported in approximately 20 percent of patients treated with either drug.<sup>96</sup> Toxic hepatitis, bone-pain hyperostosis, headache, intracranial hypertension, decreased night vision, and increased triglycerides and cholesterol are also associated with their usage.

Etretinate and acitretin are both contraindicated in pregnancy. Birth defects associated with etretinate therapy include meningomyelocele, craniofacial and skeletal abnormalities, and brain defects. Because of its long elimination half-life, the recommended post-therapy contraception period for etretinate is two years. The finding that etretinate is formed from acitretin in the presence of ethanol and subsequently stored in adipose tissue<sup>97</sup> resulted in the initial two-month post-therapy contraception period for acitretin being changed to three years. The embryotoxicity and teratogenicity of acitretin

has been demonstrated in mice, rats and rabbits at 3, 15, and 0.6 mg/kg, respectively.<sup>60,98</sup> In humans, teratological effects have been reported with etretinate<sup>99,100</sup> and acitretin.<sup>101</sup>

## 20.29 Topical Retinoids

Topical tretinoin, the all-trans form of retinoic acid, is used in the topical treatment of acne vulgaris. Adverse reactions appear to be limited to local dermatological effects—such as erythema and blistering—with the incidence of these effects being increased upon exposure to UV light. The risk for teratogenicity with topical tretinoin has been estimated to be close to zero, due to limited absorption of the drug across the epidermis. However, one report describes an ear malformation in the child of a woman who had used tretinoin (0.05%) in the first trimester of pregnancy.<sup>102</sup> Topical retinoids have also found efficacy in actinic ketosis (tretinoin, isotretinoin), plane warts (tretinoin 0.05%), actinic cheilitis (tretinoin 0.1%) and stretch marks (tretinoin 0.1%).

## 20.30 Future of Retinoids

Fenretinide is one of the most promising retinoids for human chemoprevention, with its unique mechanism of action. Fenretinide has been found to have significant chemo-preventative activity in a variety of systems, including prostate, bladder, lung, oral, breast, and ovarian carcinogenesis. Fenretinide induces apoptosis (cell death) in a multitude of cell types, including bladder cancer and leukemia.<sup>103</sup> Human trials have been conducted in oral premalignant lesions, which are related to bladder carcinogenesis through etiological effects of tobacco, and results show fenretinide's activity in preventing new lesion development after primary oral-lesion resection. Two complimentary National Cancer Institute-supported placebo-controlled trials will have a huge impact on the future of fenretinide in bladder-cancer control.

Isotretinoin has shown its potential in the therapy of various neoplastic conditions, including basal-cell carcinoma, cutaneous T-cell lymphoma, and promyelocytic leukemia.<sup>104</sup>

A significant role of topical retinoids in the future lies in the cosmetics area—particularly that of aging and photo-aging. Daily application of 0.1% tretinoin cream leads to significant improvement of wrinkling and hyperpigmentation by sixteen weeks.

## 20.31 Conclusion

While the future may hold interesting possibilities for the therapeutic uses of the retinoids, the present ambiguity about therapeutic versus potential hazardous side effects of these retinoids shows that a greater level of scrutiny needs to be given to adverse reactions. Given the increasing reports of depression and suicide associated with Accutane, special care must be exercised in prescription and in monitoring.

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