Acta Derm Venereol (Stockh) 1989; Suppl 144: 7–9

Atopic Dermatitis: a Love Affair

Memories and Reminiscences

WALTER C. LOBITZ JR, M.D., L.L.D. (hon.)

Emeritus Professor of Dermatology, Oregon Health Sciences University, Portland, Oregon, USA

I fell in love with Atopic Dermatitis (AD) almost at first sight. We met for the first time in the summer of 1942 when I began my dermatology training at the Mayo Clinic. I was fascinated by the paradoxical extremes that occur in that disease: eczema in a person with the wheal and flare phenomena of atopy; vasoconstriction, facial pallor, erect nipples and erector pili contractions in a person whose trunk and extremities are reddened with vasodilation and inflammation; intense, tiny pruritic papules, some follicular and whealing, perhaps of cholinergic origin, when all else seems adrenergic and contracted: a tired face, older than its years, with infraorbital darkening and wrinkled skin in a person who is not yet 20 years old.

But most of all, I fell in love with the people who get the disease. When these individuals are well, they are bright-eyed, enthusiastic people relating well to others, being kind, helpful and cooperative. But when these individuals are sick they are miserable, resentful, hostile, selfish, uncommunicative and withdrawn. In the USA we describe this sick AD patient as having "face of a 'Wooden-Indian' ".

Let me explain: ... Tobacco and smoking was introduced to the Caucasian or so-called "civilized world" by the North American Indian and thus, the American Indian became the early symbol of the tobacco industry. During my grandfather's and father's lifetime the Tobacco Shops and Cigar Stores in the USA could be easily identified because outside of their entrances a statue of an American Indian, carved out of wood was sitting or standing; and sometimes holding a pipe or cigars. These statues are now only found in museums or in the shops for antique collectors. They are rare and quite valuable.

Let me show you one of these statues. I am certain that you, too, have had AD patients sitting before you who looked as cautious and reserved as this man ...

As you know, in 1892, AD was most comprehensively described by Besnier and even today, in Europe, "Prurigo Besnier" is an affectionate term that is still in use ... In 1902 Brocq added the name "Neurodermatitis Disseminata" ... And in 1933, although Sulzberger and Wise created the name "Atopic Dermatitis", which we now use, only he and a few of his NYC colleagues were using that term when I entered dermatology in 1942. At that time the official and accepted name in the USA was Disseminated Neurodermatitis, the same name that Brocq had introduced 40 years earlier.

This is understandable because in those days before the discovery of antihistamines and corticosteroids, the only long term approach to treatment, other than topical therapy, was a psychiatric one which we would now call "Behavioral Modification" since very deep probing of the psyche had to be a Freudian analytical approach which was not successful and sometimes even harmful to AD.

In the mid 1940s, a Dr Carl Menninger, one of America's finest psychiatrists, studied AD patients with us at the Mayo Clinic. At the end of one month he concluded that the severe AD itching was far too great a barrier to allow any proper psychiatric evaluation and treatment. What we needed, he exclaimed, was an anti-itch drug as effective and as specific as morphine was for pain. And, of course, we still do!

There was no question that the treatment and prevention of itch was our most difficult problem. It was already known that if the AD patients did not itch they usually would not scratch; and if they did not scratch they would not injure nor lichenify and sometimes would not even eczematize their skin.

In 1942 we always had at least 10–15 severe AD patients in the dermatology hospital at the same time. Their nocturnal scratching sounds were Symphonies of Percussion! ... The "rubbers" (those who rubbed their skin) made the caressing sounds of rubbing two pieces of leather together, the "scratchers" and "rakers" made the sound of scratching on sandpaper, the "patters and slappers" made the staccato notes of drumming and the "deep diggers" kneaded their skin like bread dough. Certainly it made one think that these different responses to itching may result from different types and causes of itch; a thought still kept in mind when treating AD.

Watching AD patients be suddenly seized by paroxysms of pruritus was reminiscent of the acute asth-

matic attacks which we had always stopped by injecting an intravenous bolus of aminophylline (a treatment first reported by E. P. Epstein in 1944). I gave that same treatment to these AD patients and I was pleased that it, too, aborted the paroxysms of pruritus. But at that time we also knew that we could do the same with an intravenous bolus injection of a 10% solution of Calcium Gluconate which made the patient gasp and feel warmly relaxed. We wondered whether we were merely distracting the patient with a bolus-type of injection because when we diluted the aminophylline and dripped it in slowly over a period of time there was no effect in treating or preventing the itch. Had we known then what we do now about the pharmacology of AD we would have persued that approach to treatment, but Cyclic-Amp, calcium binding proteins, etc., were not to be discovered for many years.

In the early 1950s I was trying to atropinize a local, 5 centimeter area of uninvolved skin on a patient with AD; I did this when we were studying the acetylcholine "delayed-blanch" phenomenon. But, I injected too much atropine intracutaneously and temporarily atropinized an AD patient who had been in remission; i.e., I induced a systemic atropinization reaction causing tachycardia, hyperventilation, severe agitation, restlessness and a diffuse, generalized, intense erythema. Previous to this moment the patient had been in a 3 month remission without any dermatitis, itching or even white-line phenomena. He immediately scratched & clawed himself all over because of intense itch. The "white-line" and the acetylcholine "delayed-blanch" reactions re-occurred everywhere on his red skin and persisted for the time it took for the atropine reaction to completely stop. Twenty four hours later the patient and his skin were back to the pre-atropinized, normal state. But with the neuropharmacology knowledge of 1951 we could not rationalize what we had done.

About 5 years later, reserpine (extracted from a rauwolfia plant) was introduced for the treatment of hypertension. Reserpine, like guanethidine, depletes stores of catecholamines in tissues, causing bradycardia and a decrease in vascular peripheral resistance, increased cutaneous blood flow and thus postural hypotension. It also causes central sedation and indifference. Side effects include flushing, nasal congestion, abdominal cramps and diarrhoea. Reserpine was also suggested for the treatment of AD. So, Dr Otis Jillson and I decided to prescribe it. But, as we always did with a new drug, Jillson and I first took the reserpine outselves in order to understand how the patient would feel and react. It takes several days for reserpine to achieve a therapeutic effect. Certainly our moods gradually flattened, but at the same time our noses became stuffy and all of our skin flexures warmed, became red and mine even itched (I think I am an unerupted, red-faced atopic and I am sure that I carry that gene). Then we gave the reserpine therapy to three patients with mild AD, who were friends and professional colleagues and interested in its possible benefit.

Unfortunately there not only was no benefit, but within a week, all three patients had severe, generalized flares of their AD. It took a month of intensive topical therapy before we could bring them back to a pre-reserpine state. By then, we had suspected that acetylcholine stimuli and cholinergic emotions could flare AD. But we were not clever enough to recognize that we, personally, had experienced acetylcholine-like effects from the reserpine. Later, in retrospect, we wondered if that was why our AD patients were made worse by it.

Subsequently, I have had several former AD patients, who were well into middle age and had lived decades without any dermatitis, suddenly develop AD again after receiving reserpine treatment by family doctors for "stress" hypertension. Stopping the reserpine always stopped the dermatitis.

Recall that AD patients are hypotensive at rest, but they respond with hypertension to the "cold-pressor" stress test! This was first described by Eyster, Roth and Kierland in 1952 when we were all just beginning to define a few of the physiologic and pharmacologic AD paradoxes; acetylcholine's "delayed blanch" was another. But we did not know how to interpret these cholinergic and adrenergic responses, nor how to interpret the blocking or enhancing effects of drugs such as atropine, nicotine, reserpine, histamine, etc., some of which I have already mentioned. Cyclic AMP & GMP, were unknown to us, then, as were cellular and humoral immunity, IgE, T-cells and B-cells, etc. They were yet to be discovered ... And we knew that allergy was somewhere in the picture because we had also seen AD patients made worse with antigenic vaccines used to treat their concomitant atopic asthma and rhinitis. But we did not know where to fit it into the puzzle ... And although we knew that atopy "ran in families" the sciences of modern genetics were just beginning to evolve.

Then came the 1960s when we were inundated with new knowledge in all these basic sciences areas. And

we tried, each in one's own way, to apply the excitement of these new concepts to AD ... It was not until 1968, when Szentivany's hypothesis suggested atopy might be a disease of defective beta-adrenergic receptor function, that the door was opened for many of your own accomplishments in the 1970s.

Now, in the 1980s we all know, for example, that there is an excess of phosphodiesterase and hyper IgE in active AD. And we know that many other pieces of new information from many different scientific areas are being added, by you, to solve the AD puzzle (e.g.: Type I Immunology, Cell Mediated Immunity, B and T cell interactions, the role of macrophage monocytes and Langerhans cells, cellular genetics, etc.). But where they fit and how they affect each other is not yet completely clear.

And now as we ... No, I should not say 'we' ... And now as '*You*' move into the 1990s let me assure you that I (this 76 year old 'lover' of Atopic Dermatitis) am very excited and I am assured and therefore quite content that all of you, the younger AD 'lovers', 'wooers' and 'courtiers', will make the complex AD facets interrelate, fit and fuse together into a clearer picture; also, that 'Your' students, the AD courtiers of the future, will carry on into the 21st century, putting the finishing touches to the portrait of our loved one, Atopic Dermatitis!

Thank you very much for allowing me to join you here in Oslo, to reminisce a little and to wish you well!