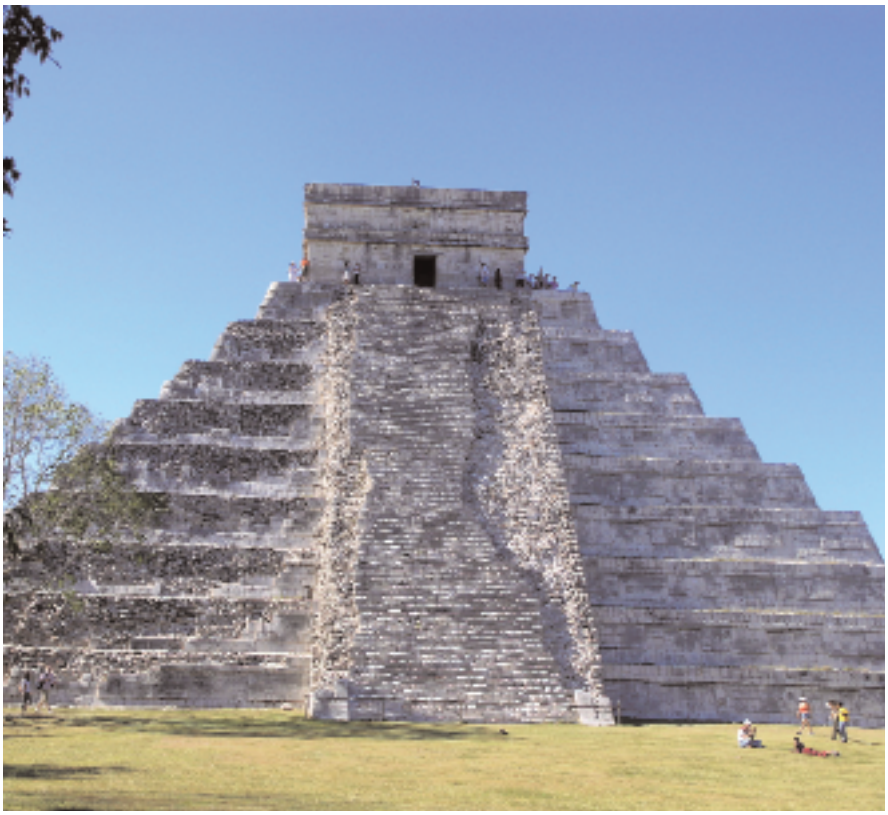
ALLERGEN Focus



Focus on T.R.U.E. Test Allergen #24:

Thiuram

BY SHARON E. JACOB, M.D., AND OTOBIA DIMSON, M.D.

Allergic contact dermatitis (ACD) is an important disease with high impact in terms of patient morbidity and economics. The contact dermatitides include allergic contact dermatitis, irritant contact dermatitis and contact urticaria.

Irritant contact dermatitis, the most common form, accounts for approximately 80% of environmental-occupational based dermatoses.

Contact urticaria (wheal and flare reaction) represents an IgE and mast cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis; the foremost example of this would be latex hypersensitivity. While this is beyond the scope of this section, we acknowledge this form of hypersensitivity due to the severity of the potential reactions and direct the reader to key sources.[1,2]

Allergic contact dermatitis represents a T helper cell Type 1 (Th1) dependent delayed-type (Type IV) hypersensitivity reaction.

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The instigating exogenous antigens are primarily small lipophilic chemicals (haptens) with a molecular weight less than 500 Da. Unlike other haptens, metal antigens do not covalently bind to carrier proteins; instead they complex with proteins similar to the binding of cobalt and vitamin B_{12}.[3]

On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated that includes cytokines, i.e. interleukin 2 (IL-2) and interferon gamma (IFN-g), T cells and Langerhan cells. This complex interaction leads to the clinical picture of ACD.

The primary focus of this section is to highlight the educational component of allergic contact dermatitis.

CLINICAL ILLUSTRATION

We report a case of a woman who was referred to the Contact Dermatitis Clinic at the University of Miami with generalized pruritus. During the interview she reported wearing a make-up sponge in her shoe to relieve pressure from her callus. On physical examination, we noted erythema at the site of application of the make-up sponge.

THE HISTORY OF RUBBER

Rubber held a central role in the religious and political culture of the early Mayans. In the story of the Popol Vuh, this significance was underscored as the ball playing hero twins, Xbalanque (deer jaguar) and Hunahpu (hunter), conquer the underworld death deities in a contest utilizing solid, black, heavy rubber balls on an "I"-shaped ball court. This mythical story is the foundation for the Mayan religious-cultural practice carried out in the traditional Tlachtli game and its post-game sacrifice.[4,5]

A DEADLY GAME

Since the second millennium B.C., the Tlachtli game has been cited as a

cross between modern competitive sports of soccer, basketball and football in which bouncing balls are utilized. The cultural popularity of this game is visible by the more than 200 practice arena/ball court ruins in Arizona alone. This very popular game was played with a bone breaking, 8-pound, black rubber ball, notably the size of a bowling ball or human head (a constant reminder of the cost of defeat). In this game, much like in the Roman amphitheaters, aristocratic Mayan warriors competed against unsuspecting teams of war captives. The winning team was proclaimed victorious when one of its players successfully put the ball through a raised stone hoop at the opposing end of the court.[4,5]

As with soccer, the players could only hit the ball with their torso, hips and shoulders while avoiding contact with their hands. At the end of the game, the losing team players were ceremoniously sacrificed through a decapitation service in the honor of Amapan and Uappatzin, the patron deities of the ball court, and Huitzilopochtli, the Aztec god of war.

In the Chichen Itzan capital, the importance of the game is exemplified as the largest and better-built Mayan ball courts are found at the centers of ceremonial precincts such as the Temple of the Jaguar, where the sacrificial ceremonies took place.

It is known that the Tlachtli game held economic and political significance as well. Spectators gambled for valuable textiles since currency wasn't in existence at the time. After a point was scored during a game, the spectators threw their robes at the players to pay their bets and fled to cut their losses.[4,5]

EARLY INDUSTRIAL USES OF RUBBER

At the turn of the sixteenth century, as Nicolaus Copernicus theorized that the earth moved around the sun and Leonardo da Vinci painted the Mona Lisa, the Spanish explorers to the "New World" were introduced to the novelty of solid *rubber* bouncing balls. They brought this amazing item to Europe for use as sporting balls, human figurines, coating for wooden tool handles, paints, and medicines.

The Meso-Americans isolated raw liquid rubber (latex) from the soft bark of the *Castilla elastica* tree. Also indigenous to Central and South America were the jungle vine saps, which were added to the latex, heated, and shaped into rubberized polymer balls.

IN THE ANCIENT MAYAN GAME OF TLACHTLI, WHICH WAS PLAYED WITH A BONE-BREAKING, 8-POUND, BLACK RUBBER BALL, LOSERS WERE CEREMONIOUSLY SACRIFICED THROUGH A DECAPITATION SERVICE . . . .

It is now known that the vine sap contained sulfur organic groups that cross-linked molecules in the rubber latex during heating, conferring strength, elasticity, and a 3-D configuration to rubber latex, a process later termed "vulcanization".[6]

Interestingly, not until 1770 was dry latex known as "rubber", a term accredited to British chemist Joseph Priestley, who made the important discovery that rubber could rub out pencil marks.[7]

PERFECTING THE PROCESSING OF RUBBER

By the early nineteenth century, rubber was well established as a flexible, tough, waterproof and air-impermeable material with great potential utility.

Commercial exploitation, however, was halted by the fact that rubber's toughness and elasticity made it difficult to process. In addition, the formulation and stability of rubber over a range of temperatures was not optimized. Rubberized articles became stiff and hard in cold weather, and soft and sticky in hot weather.

The quest to make useful goods from rubber led Thomas Hancock of Great Britain to invent the all-purpose rubber band. The popularity of the rubber band was such that Hancock later invented a machine, the masticator, to facilitate rubber processing. By subjecting the rubber to intensive shearing, it was found that the product was softened and more amenable to mixing and shaping.

CREATING RUBBER WITH THIURAM

Nevertheless, rubber's propensity to crack in cold weather and melt in heat remained until an American, Charles Goodyear, discovered vulcanization in 1839. His accidental over-heating of a mixture of rubber, white lead and sulfur led to the discovery of a new rubber mixture that maintained structure and stability over a wide range of heating and cooling conditions, an ideal characteristic for automotive tires. With reference to their paramount inventions, Charles Goodyear and Thomas Hancock are both charged with patenting the process that was subsequently defined as "vulcanized rubber".[8]

Of interest, the term "vulcanization" gives reference to Vulcan, the Roman god of the underworld's blacksmith. Given the high heat process in which rubber chemicals were compounded with sulfur, Vulcan came to symbolize the process through which the door to the enormous market for rubber goods was opened.[9]

In the early 1900s, the process of vulcanization was refined with the development of chemicals that could accelerate the polymerization of the latex isoprene monomers into pliable and stable rubber compounds. Even with elevated temperatures, the rate of vulcanization with sulfur was slow.

To overcome this obstacle, Goodyear

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TABLE 1

PRODUCTS CONTAINING THIURAM

Rubber products (gloves, shoes, make-up sponges, bunion pads, toothbrush handles, baby bottle nipples, pacifiers, sports shoes, eyelash curlers); Crepe soles (neoprene)
Adhesives; stethoscopes; ear plugs; dentures; dental dams
Veterinary soaps and shampoos
Contraceptive/pleasure devices: (condoms, diaphragms); rubber vibrators
Animal repellents: fungicides; germicides; insecticides; pesticides; disinfectants
Preservatives (woods, paints, greases, lubricating oils)
Food wrappings; food handled with latex gloves
Medications (antabuse, scabicide, sunscreens, surgical wraps, fungicide)
Polyolefin plastics (anti-oxidants); putty; tool handles

employed the use of oxides of lead, magnesium and calcium, until 1906, when the organic accelerators were discovered. Aniline was the first, followed by N,N-diphenylthiourea, hexamethylenetetramine, and the dithiocarbamates (which are oxidized to thiuram disulfides).[10]

With the advent of the organic chemical accelerators, such as thiuram, the vulcanization process was expedited. The principle thiurams used industrially are tetramethylthiuram monosulfide (TMTM), tetramethylthiuram disulfide (TMTD), tetraethylthiuram disulfide (TETD), and dipentamethylenethiuram disulfide (PTD). Today, they are among the most frequently used rubber accelerators in the manufacturing of gloves. Numerous other consumer products also contain thiurams ***(see Table 1)***.[11]

WHO'S MOST AFFECTED BY THIS ALLERGEN?

As early as the 1920s, thiuram was found to cause eczematous eruptions in rubber industry workers.[12] Today, there is an increasing incidence of thiuram allergy among healthcare workers. As much as 33% of this group may suffer from thiuram-related hand dermatitis, correlating with the Universal Precautions Mandate for use of powdered latex gloves in the early 1990s.[13]

In the 1930s, the agricultural industry discovered an enormous use for thiuram as a powerful germicide, fungicide, seed protectant and animal repellent. As such, it was used in soaps, sunscreens, and to preserve fabric and wood products.

IN THE 1930s, THE AGRICULTURAL INDUSTRY DISCOVERED AN ENORMOUS USE FOR THIURAM . . . . IT WAS USED IN SOAPS, SUNSCREENS, AND TO PRESERVE FABRIC AND WOOD PRODUCTS.

Furthermore, it was widely dusted and sprayed on farmlands, lawns and golf courses. Subsequently, allergic contact dermatitis to thiuram was cited in dock laborers unloading bananas, golfers, gardeners and florists.[14] In fact, thiuram is an EPA-approved fungicide with tolerances specified for residues in or on raw agricultural foods for apples, celery, peaches, strawberries, tomatoes, bananas and onions.[15] Thiuram may also leak into food, milk and water from rubber in food containers.

The medicinal uses of thiuram were pursued in the early 1950s. Danish psychiatrist Martensen-Larsen, while exploring the ethyl analogue of thiuram as a possible vermifuge (intestinal worm expellant) in man, came upon an unusual fact. Ingestion of a small amount of disulfiram (TETD, Antabuse) produced a violent physical reaction of nausea, vomiting, and rapid changes in blood pressure when combined with alcohol. This led to its use, beginning in the early 1950s, as an effective dissuader for alcoholics. Theoretically, thiuram accelerators inhibit the complete enzymatic oxidation of ethyl alcohol in the liver resulting in the accumulation of acetaldehyde in the blood causing unpleasant side effects. It is important to note that, as early as 1962, thiuram-rubber sensitized individuals developed generalized dermatitis following the ingestion of Antabuse.[16]

Recently, allergic contact dermatitis to thiuram mix has been linked to henna-based tattooing art. Henna, a powder extracted from the leaves of the shrub *Lawsonia inermis*, is used to temporarily tattoo the skin and dye hair reddish brown.

It is postulated that the exposure relates to the tattooing process of guided stick-on rubber stencils, which are applied to the skin prior to dyeing with black henna. In addition, henna tattooing has the potential to cause allergen sensitization to para-phenylenediamine (June 2006 "Allergen Focus" article) and to natural rubber latex proteins found in the commercially available rubber stencils.[17]

TESTING FOR THIURAM SENSITIVITY

Patch testing for thiuram allergy can be accomplished with the commercially available Thin-layer rapid use epicutaneous (T.R.U.E.) test. Thiuram mix (site #24) is composed of equal quantities of the top-four utilized thiuram chemicals (three disulphides and one monosulphide): tetramethylthiuram disulfide (TMTD), tetraethylthiuram disulfide (TETD), tetramethylthiuram monosulfide (TMTM), and dipentamethylenethiuram disulfide (PTD).

Another investigational tool to confirm thiuram contact dermatitis is the lymphocyte transformation test (LTT). In this test, the polymorphonuclear (immune) cells of thiuram patch-test-positive patients will exhibit significant cellular proliferative responses to tetramethylthiuram monosulfide (TMTM) and tetramethylthiuram disulfide (TMTD) conjugates when challenged, compared

with control donors with no history of allergic contact dermatitis.[18]

To discern which rubberized items contain thiuram, products can be tested by extraction with acetone and cuprous acetate. When thiuram is present, the color changes from blue to mint green to dark green, which indicates a positive reaction.[19]

THE VALUE OF THIS PATIENT CASE

Our patient tested positive for thiuram. She was educated on removing unnecessary rubberized articles/chemicals from her environment, such as the make-up sponge and rubberized toothbrush handle. Upon follow-up to clinic after an 8-week avoidance regimen, the pruritus had mitigated.

This case underscores the importance of appropriate patch testing and subsequent patient education. Once an allergen is identified, patient education is of the utmost importance, because the mainstay of treatment for allergic contact dermatitis is avoidance. ■

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