

ALLERGEN Focus



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Focus on T.R.U.E. Test Allergens #19 and #22 — Mercaptobenzothiazole and Mercapto Mix

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The thin-layer rapid-use epicutaneous (T.R.U.E.) test is a valuable first-line screening tool used by many dermatologists. Although the test focuses on common allergens, frequent questions have arisen from colleagues and patients as to where a specific allergen is derived or what products patients should avoid. With this in mind, this column was developed to provide educational information about the T.R.U.E. test allergens.

THE CONTACT DERMATITIDES

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

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 being 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 (ACD) affects more than 70 million Americans each year and has a high impact both in terms of patient morbidity and economics. The primary focus of this section is to highlight the educational component of this important inflammatory disorder.

CLINICAL ILLUSTRATION

A pediatric patient who was suffering with plantar hyperhidrosis and severe eczematoid dermatitis of the soles presented to the University of Miami Allergic Contact Dermatitis Clinic for evaluation. Notably, he constantly wore either sneakers or rubber sandals.

HISTORY OF SHOES IN THE GAMES

The first recorded Olympic games were held in Olympia, Greece (c.776 B.C.), although Homer's *Iliad* suggests they began much earlier. At the inaugural games, Korobos, the cook from Elis, was the first documented Olympian to have placed first in the "stade" foot race (approximately 192 meters), which notably was run *barefoot*.³

In these ancient games, all contestants had competed devoid of any sportswear, including footwear. As the Greek Empire grew, many athletes traveled from the colder distant outreaches of the Empire to compete in the games. Often, these competitors wore sandals.⁴

Initially, spectators and barefoot tradi-

tionalists teased the outlandish foreign contenders.⁴ When the sandal-clad athletes dominated the games, however, the public grew suspicious and viewed the wearing of shoes as cheating.⁴

Eventually, it was recognized that the sole of the sandal increased ground traction, allowing for greater forward propulsion. The overall higher performance of the sandal-wearing athletes inspired the acceptance of a running sandal as standard athletic gear.

Between the Greek and Roman Empires, in the region presently known as Northern Italy, a small civilization known as the Etruscans once existed.⁴ The revered Etruscan sandal artisans had revolutionized the sandal with their novel technique of metal tacking the sole of the sandal to the upper part of the shoe.⁴

With the expanse of the Roman Empire, the Olympic Games had become a Roman tradition. But when Christianity became the official religion of the Roman Empire, the Olympic Games fell out of favor and were touted as a pagan festival in disagreement with Christian ethics.³

By 392 A.D., anti-pagan sentiment grew in fervor, leading Emperor Theodosius to outlaw the Olympics and to end what is thought to have been a 1,000-year-old tradition.³ Furthermore, the banning of the games and the fall of the Roman Empire devastated the booming Etruscan Shoe Industry, and the craft of sandal making was almost lost.⁴

RUBBERIZED SHOE INNOVATIONS

Although sports were played throughout the Middle Ages, the open sporting competitions held in the British Isles and Empire in the 17th and 18th centuries were used to unite the kingdom (U.K.).³

Athletes competed in non-water-proofed leather tightly fitted shoes, which stretched with wear making them useless for running multiple races.⁴

In 1832, Wait Webster was the first to patent a process whereby rubber soles could be attached to shoes and boots for durability and traction.⁴ It wasn't until 1867 that this innovation was implemented in a croquet shoe, introduced by Candee Rubber Co. of Norwich, CT.⁵

The novel shoe had a rubber sole and lightweight canvas uppers and was considered a luxury item of the rich and famous.⁵ Movement in the shoes was so noiseless on most surfaces that they became popular among *sneak thieves*, and thus the shoes began to be known as "sneakers".⁶

SNEAKERS BECOME POPULAR

The first mass marketed sneaker was sold by the Liverpool Rubber Company (later Dunlop) in Great Britain (c.1876).

This canvas upper and rubber soled beach "sand shoe" could be worn interchangeably on the right or left foot and was developed for shoe "training" in children (c.1830).

By the 1870s, the incredibly popular shoe acquired the nickname "plimsoll" because the colored horizontal band joining the upper to the sole resembled the plimsoll line on a ship's hull.⁴

The growing popularity of sneakers had not gone unnoticed. In the United States, the merging of nine small rubber manufacturing companies (from 1892 to 1913) led to the formation of the United States Rubber Company and the promotion of a new Goodyear Company children's shoe. As "Peds" (the Latin term for foot) was already taken by another manufacturer, the new kids shoe line was called "Keds".⁷

REVIVAL OF THE OLYMPICS

Around this time, Frenchman Baron Pierre de Coubertin became convinced that "sport is the springboard for moral energy," and he set forth to unite the trading nations on the athletic field in Athens, Greece. His dream was realized with the revival of the Olympic Games in April of 1896.⁸

In 1928 at the Amsterdam Olympic Games, Adi Dassler realized his own dream, as he introduced the first shoe designed specifically for track and field events.⁹ At the age of 20, he had constructed this prototypical sports shoe with post-war limited materials in his mother's washroom (canvas, cotton lace, rubber and glue.)

Amidst the Great Depression, the 1932 Olympics struggled to take place, with notably less than half the usual athletes and spectators in attendance.

Yet, Dassler was determined to be the first entrepreneur to use sports to promote public awareness of his innovations. His mission was to invent the quintessential athletic shoe, which would mold to the athlete's foot and remain light, functional and durable, while also enhancing performance.⁹ And in 1936, by good fortune, a revitalized Olympic games took place in Berlin providing German Dassler, an avid athlete himself with the opportunity to closely interact with these sports participants.

Ultimately, nearly every Olympian wore a pair of Dassler's popular shoes at the '36 Olympic games.¹⁰ Furthermore, young hero Jesse Owens, clad in a pair of Adidas running shoes, captured four gold medals for the United States.

VULCANIZATION OF RUBBER

By the time the Goodyear shoe company had regrouped for Keds, Charles Goodyear was no longer in the company picture. Despite his fundamental and incidental discovery of vulcanization (the chemical process of making naturally soft rubber into an elastic weather-proof material) in 1839, Goodyear died a penniless man.¹¹

As Charles Goodyear and Thomas Hancock are both charged with patenting the process of vulcanized rubber, it was Hancock's filing for the patent a few weeks earlier in 1844 that had ensured his success.¹¹

Over the last century, the vulcanization process was modified to include a variety of sulfur-containing accelerating agents that allowed for lower heat and more efficient vulcanization with a more durable outcome product.¹²

UTILIZING THE RUBBER ACCELERATOR MERCAPTOBENZOTHIAZOLE

Mercaptobenzothiazole (MBT) is a commonly used sulfur-containing rubber vulcanization accelerator.¹³ (*See Tables 1 and 2*) As early as 1934, rubber-associated allergic contact dermatitis to MBT was reported.¹⁴ MBT is present in many shoes and is used in a rubber adhesive to cement shoe linings to shoe uppers.¹⁵ It is important to note that since MBTs are commonly used in rubber insoles, MBTs were among the first

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TABLE 1: POTENTIAL EXPOSURES TO MBT IN THE WORKPLACE AND THE HOME ADAPTED FROM 1,13,17

Antifreeze	Conveyor Belts	Garden Hoses	Rubber Accelerator
Adhesives	Cutting Oils	Gas Masks	Rubber Bands
Anti-Corrosive Agents	Cements (<i>Contact, Plastic, Rubber, Shoe, Waterproofing, Tile, Thermoplastic</i>)	Glue for Leather	Rubber Pillows
Anti-Slip Carpet Backing	Dental Dams	Gloves	Rubber Sheeting
Aprons	Detergents (<i>Granulated and Tablets</i>)	Greases (<i>Heavy Duty</i>)	Safety Goggles
Balloons	Diaphragms	Lining of Fuel Tanks	Shock Absorbers
Black Tires	Earphones	Mats	Slippers
Boots and Shoes	Elastic in Hairnets	Mattresses	Sponge Makeup Applicators
Brassieres	Electrical Cords	Non-Slip Waistbands	Support Stockings
Caulking	Erasers	Paints (<i>Black Tire</i>)	Swimwear
Cleansers (<i>Auto Cooling Systems</i>)	Film Emulsions	Photographic Film Emulsion	Tires and Tubes
Clothes	Fungicides	Pottery Mold Releasing Fluid	Toys
Condoms		Plugs	Veterinarian Medications

TABLE 2: PRODUCTS CONTAINING MERCAPTOBENZOTHAZOLE ADAPTED FROM 13,17,25

GLOVES	LOTIONS
Chloroflex	Cal-pox Lotion,
Conform	Happy Jack Skin Balm
Dermaclean	Mercaptocaine
EP Surgical Style	
Esteem	FUNGICIDE/MICROBIOCIDE*
Maxxus	Betz Algicide (Tx-P)
Microtouch	Gormel's Complete Rose Spray
Multiflex	Rx-15, Rx-29, and Rx-35
N-Dex	Slime-Trol
Neutralon	Slimicide D-2
Nitratex	Tree-Top Spray
Nitricare	Vancide 26EC, 20S, 26, 51, and 61Z
Nitrisolve	Veterinary Medications
Nitra-touch	Analan Ointment 2%
Perry	Caladerm Ointment 1.25%
Savacare PCI	Delcreo Penetram Skin Balm 1%
Sensicare	Dr. Merrick's Sulfodene Preparation 1.25%
Sensitouch	Legear Flea and Tick Powder 1%
Triflex Orthopedic	Mercaptocaine 2%
Ultraflex	
Ultralon	OTHER
Uniseal Nitrile	NACAP (Corrosion Inhibitor)
VHA Plus	Mobil Rubber Lubricant
Vibrex	Rubber Earplugs
Vitron	Neoprene Splints

*Salts of MBT when used to prevent mildew in fabrics or as an algicide or slimicide, may not be as prone to cause ACD as MBT in rubber.

allergens identified as a cause of rubber footwear dermatitis.¹⁵

Physician Etain Cronin first noted a rising trend toward rubber chemical allergies (away from leather-based chemicals) in shoe-associated contact dermatitis between 1960 and 1965 at St. John's Hospital in London. Among 100

patients who had positive reactions to rubber in their shoes between 1953 and 1965, Cronin found that 45% were MBT-positive.¹⁶

Because of its use in shoes (an ideal environment with humidity and occlusion), MBT is one of the most common sensitizers in childhood, particularly in

boys who have hyperhidrosis. Notably, it has also been a culprit in infant-acquired shoe ACD.¹⁷

Regardless of where the rubber is located within the shoe, it should be noted that when the shoe becomes wet (after being worn), suspect chemicals may migrate to distant parts of the shoe. Paul V. Marcussen demonstrated that MBT could diffuse out of rubber and into canvas by co-immersion of the two for 24 hours.¹⁸

This important discovery underscores that sensitized patients need to be aware that socks and stockings worn with shoes that contain MBT chemicals can become permanently contaminated by the rubber chemicals, and thus should be regularly replaced.

It is also important that patients with foot dermatitis not wear shoes against bare feet.¹⁵

Furthermore, wearing down the heel pad or lining of a shoe will expose the adhesive and can cause dermatitis in susceptible people. Sensitive patients should be cautious of rubber insoles for shoes such as orthopedic inserts (the "Vy-Foam" urethane foam insole by Dr. Scholl does not contain MBT), rubber boots, rubber cements used in joining shoe uppers, the outer leather and linings, and rubber box toes.

Patients may switch to all-leather accelerator-free shoes, for example, moccasins (L.L. Bean deer hide), or shoes with all wool or cork insoles secured by fish glue. Plastic-molded accelerator-free sandals for women may

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be obtained from Sandak, Kinney or Bass Weejuns.¹⁹

UNEXPECTED EXPOSURES TO MBT

MBT has been reported as a contaminant in a variety of injectable medications (e.g. digoxin, sodium pentobarbital, epinephrine, lidocaine hydrochloride, mepivacaine hydrochloride, pilocarpine hydrochloride, and dexamethasone sodium phosphate) and blood draw samples.²⁰

An evaluation determined that the MBT contamination originated from the rubber closures on the single-dose delivery syringe or syringe cartridge, and the amount extracted appeared to be dependent on the level of MBT in the rubber, not on the composition of the solvent for the drug.²¹ Furthermore, MBT has been found in aqueous extracts of rubber bottle nipples and diapers.

This chemical has also been implicated as one of the allergens responsible for “Lucky Luke” contact dermatitis, which was first described in 1998 by Roul et al.^{22,23} Lucky Luke was a popular French cartoon character created by Maurice De Bevere in 1948 for *Le Journal de Spirou*. Set in the American Old West, the cartoon features Luke — the world’s greatest, luckiest cowboy, who could outride, outdraw and outshoot anyone.²³

This type of diaper dermatitis is caused by the anti-leak rubber component system for active toddlers, which produces a particular dermatitis pattern reminiscent of a cowboy’s gun belt holsters, thus the association with Lucky Luke.²⁴

THE SPANDEX REVOLUTION — UNFAIRLY JUDGED?

Cloth-covered foam materials and clothing that contains spandex are other possible sources of MBT exposure.²⁰ Spandex, developed by American scientist Joseph C. Shivers, was the first manufactured non-rubber elastic fiber introduced by DuPont (Lycra c.1958).

This polyurethane fiber chain allows stretchability up to 600 times the resting length, and the capacity to return to its original size.²⁰ Lycra is lightweight and resists decomposition when exposed to perspiration, body oils, dry heat, skin lotions, perfumes, and detergents.²⁰



DURING AN ACCIDENTAL MIXING OF CHEMICALS ON A HOT STOVE, CHARLES GOODYEAR HAD NOTABLY OBSERVED THAT WHEN RUBBER CHEMICALS MIXED WITH SULFUR THEY PRODUCED AN ELASTIC WEATHERPROOF MATERIAL.

The versatility and durability ensured that spandex quickly replaced rubber in women’s foundation garments. Also, the chemical composition of spandex allowed for better dyeability and blending with other natural and synthetic fibers such as cotton, wool, silk, and linen to increase its stability and durability.²⁰

This discovery revolutionized the fashion industry, launching the new comfort era. The 1960s saw a boom in soft-support pantihose and ladies’ undergarments, followed by figure-flattering swimwear and skiwear, made

popular by the French Olympic ski team. By 1967, Spandex-associated ACD was seen. Primarily, it was the MBT used in manufacturing spandex that was responsible for the allergic reaction to spandex garments.²⁵

Bicycle racers sported aerodynamic spandex shorts in the 1970s, which was later topped by the fashion boom in dancewear (leotards, tights and legwarmers), stretch jeans, and the quintessential jogging suits of the 1980s.²⁰

Physician J. Blair Pace was among the first to describe ACD to spandex devoid of MBT. He noted dermatitis that worsened with the consumption of alcoholic drinks (a hallmark side effect to thiuram-based chemicals).

Thiuram, another sulfur-containing rubber accelerator, was found to be the culprit allergen.^{14,17} More on thiuram can be found in the February 2006 “Allergen Focus” column in this journal.

TESTING FOR MBT

Patch testing for MBT allergy can be accomplished with the T.R.U.E. test — site # 19. Both MBT as well as mercapto mix (site # 22) should be selected for patch testing to increase the sensitivity of the test. The mercapto mix containing N-cyclohexylbenzothiazyl-sulfenamide, dibenzothiazyl disulfide, and morpholinylmercaptobenzothiazole has a sensitivity of 0.60, whereas MBT has a higher sensitivity of 0.69.²⁶ When these are combined, the sensitivity is raised to 0.77 for detecting contact allergies to the MBT derivatives.

Mercapto mix contains three allergens: N-cyclohexylbenzothiazyl-sulfenamide, dibenzothiazyl disulfide, and morpholinylmercaptobenzothiazole.

VALUE OF THIS PATIENT CASE

Our patient with allergy to MBT underscores the importance of appropriate patch testing and subsequent patient education.

The presence of MBT in such a wide variety of products makes it an especially common and difficult-to-avoid contactant in daily activities.

To the greatest extent possible, rubber products were removed from the patient’s daily routine, and non-MBT-containing alternatives were substituted

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TABLE 3: PRODUCTS FREE OF MERCAPTOBENZOTHAZOLE ADAPTED FROM 13,17

<p>GLOVES</p> <p>Allerderm <i>Heavy-Duty Vinyl Gloves, Vinyl Exam Gloves</i></p> <p>Allegiance</p> <p>Biogel</p> <p>Duraprene</p> <p>Elastyfree and Elastylite <i>Surgical Gloves</i></p> <p>N-Dex Free Ultimate</p> <p>Neotech</p> <p>Safeskin <i>PFE Exam Gloves</i></p> <p>Silvershield/4H</p> <p>True Advantage</p> <p>Ultra Preserve</p>	<p>INSOLES</p> <p>Dr. Scholls <i>ViFoam, Thermo-Cushion</i></p> <p>Superfeet</p> <p>Cambion</p> <p>Spenco</p> <p>Magister</p> <p>Sports Equipment</p> <p>Hedstrom sports balls</p> <p>WINN Inc. Synthetic Grips</p> <p>Speedo Swim Goggles</p>
<p>CLOTHING</p> <p>Jockey Underwear</p> <p>Pampers and Luvs Diapers</p> <p>Lycra Spandex Underwear</p> <p>Vanity Fair Spandex Garments</p> <p>Warners Spandex Garments</p>	<p>OTHER</p> <p>Condoms — <i>Fourex (Schmidt), Naturalamb Durex, Avanti, Trojan, Supra, Lambskin</i></p> <p>Kleinert's Non-Rubber Dress Shields</p> <p>Diaphragms — <i>Koro-Flex, Koromex</i></p> <p>Mylar Balloons</p> <p>Duo Brand Surgical Adhesive (<i>Johnson & Johnson</i>)</p>

TABLE 4: SYNONYMS OF MERCAPTOBENZOTHAZOLE ADAPTED FROM 27

<p>2(3H)-Benzothiazolethione</p> <p>2-Benzothiazolethiol</p> <p>2-Benzothiazolinethione</p> <p>2-Benzothiazolyl Mercaptan</p> <p>AG 63</p> <p>Accel M</p> <p>Accelerator M</p> <p>Benzothiazole-2-thione</p> <p>Benzothiazolethione</p> <p>Captax</p> <p>Dermacid</p> <p>Ekagom G</p> <p>Kaptaks</p> <p>Kaptax</p> <p>MBT</p> <p>Mebetizole</p> <p>Mebithizol</p>	<p>Mercaptobenzothiazol</p> <p>Mertax</p> <p>NCI-C56519</p> <p>Nocceler M</p> <p>Nuodeb 84</p> <p>Pennac MBT powder</p> <p>Pneumax MBT</p> <p>Rokon</p> <p>Rotax</p> <p>Royal MBT</p> <p>Soxinol M</p> <p>Sulfadene</p> <p>Thiotax</p> <p>USAF gy-3</p> <p>USAF xr-29</p> <p>Vulkacit M</p> <p>Vulkacit Mercapto</p> <p>Vulkacit Mercapto/C</p>
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instead. (See Table 3.) The patient's parents were also informed about the multitude of synonyms for the culprit allergen to aid with avoiding products that could cause reaction flare. (See Table 4.)

With this, the patient experienced significant improvement, which is consistent with the fact that the mainstay of

treatment for allergic contact dermatitis is **avoidance**. ■

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