Prick and Intradermal Allergy Testing

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Disclosure Statement

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I participate in the following Speaker's Bureau and/ or Advisory Boards:

- **Myland Labs**
- **TEVA**
- **Sunovian**
- **Sanofi**

Learning objectives

- At the conclusion of this lecture, the attendee should be able to:
  - Cite the indications for allergy skin testing
  - Discuss the process of selecting allergens to be tested
  - Describe the methods used to perform prick/puncture and intradermal skin tests
  - Compare and contrast prick/puncture and intradermal skin tests

The essential components of allergy diagnosis

Clinical History and Physical Examination

Symptoms versus Exposure

Diagnostic Confirmatory Test

Skin Test (Puncture, Intradermal)

Allergen-specific IgE antibody serology

Provocation Test

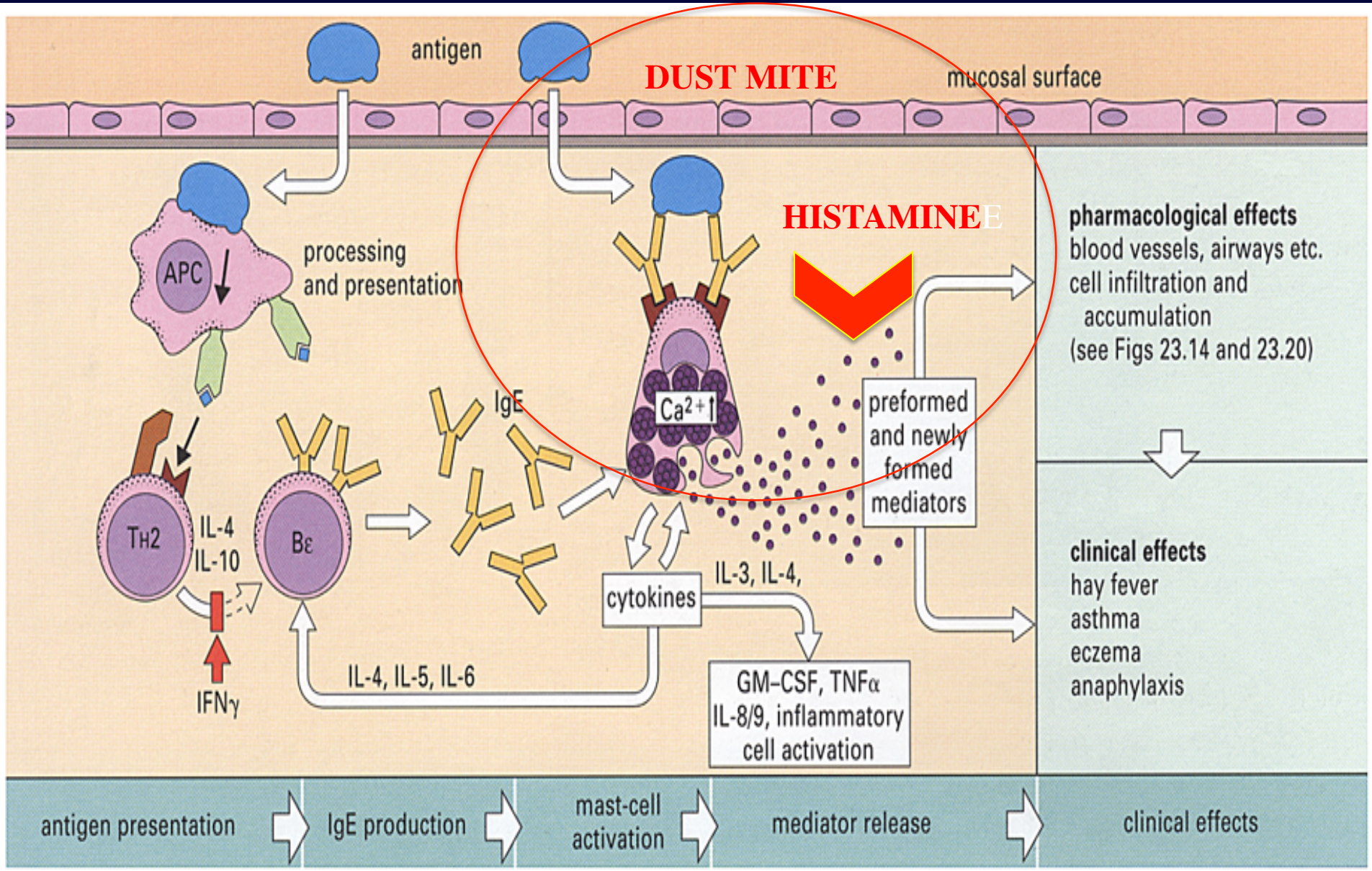
Oral, Nasal, Bronchial Challenge

Key concepts in allergy diagnosis

- Allergic history
  - Symptom complex
  - Relationship to allergen exposure
- Physical examination, looking for the specific signs of allergy
- Confirmatory allergy test
  - Skin tests – prick/puncture and intradermal
  - Specific IgE antibody serology, an accepted alternative

1. *Oppenheimer Ann Allergy 2006;S1:6-12,*
2. *Bousquet Clin Allergy 17:529-36, 1987*
3. *Cockroft Am Rev Respir Dis 135:264-7., 1987*

Pathophysiology of an allergic reaction



Skin Prick Testing

- Skin prick testing (SPT) remains the primary confirmatory test
  - Safe
  - Fast
  - Inexpensive
  - Sensitive
  - Minimally invasive
  - Correlates well with nasal and bronchial challenge

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What is an allergen?

- An antigen causing an allergic disease is called an "allergen"
- Most allergens are glycoproteins with a molecular weight of 5 to 100 kD, most around 20 kD.
- Many pollen allergens are surface enzymes
- Some food allergens are remarkably stable and are stable even after cooking
- A genetically predisposed (atopic) person can become IgE-sensitized after several years of inhaling <1 μg of grass pollen allergen per season

Spectrum of allergen sources

Allergen extracts

- An allergen extract is prepared by incubating the allergenic material in a physiological buffer (e.g., phosphate buffered saline) followed by lipid extraction
- The allergen content was commonly expressed in crude terms such as protein nitrogen units (PNU) or **weight : volume**
- It may now be expressed as micrograms of specific allergen per ml

Allergen extracts

- Several commercial extracts used in skin testing are "standardized" regarding allergen protein concentration, composition and lack of irritating contaminants.

- Standardized allergens used in the USA
  - Grass
  - Ragweed
  - Dust Mites
  - Cat

Allergen Standardization

- Many different units are used:
  - Protein nitrogen units (PNU- world wide)
  - Allergy unit (AU- U.S. FDA)
  - Bioequivalent allergy unit (BAU)
  - Biologic units (BU- Europe)
  - International unit (IU- WHO)
  - Index of reactivity (IR- Europe)
  - Specific treatment unit (STU)
  - Activity Units by RAST (AUR- Europe)

Selection of aeroallergens

- An understanding of **pollen aerobiology** and knowledge of **allergenic cross-reactivity** between regional pollinating plant families is necessary in selecting appropriate aeroallergens
  - Example: Extensive allergenic cross-reactivity exists between **northern pasture grasses**, permitting the use of a single northern grass pollen for testing in most regions outside of southern regions of North America and Europe.

Major Allergens in India

- Mesquite
- Castorbean
- Indian Elm
- Sagebrush
- Cedar
- Dust Mite
- Pigweed
- Parthenium
- Johnson grass
- Bermuda grass
- Mallotus Phillipensis

General rules for successful SPT

- It is imperative that the technician performing the skin tests as well as the clinician ordering/interpreting these tests understands the characteristics of the specific tests they are administering.
- This includes:
  - type of skin testing
  - device used
  - placement of tests (location and adjacent testing)
  - the particular extracts (source, concentration) being used
  - the potential confounder of medications that may suppress skin test response.

Suppression of skin tests by medication

- Most antihistamines and anti-depressants suppress skin tests for 3-7 days
- No significant effect of SABA, H2 antagonists, monteleukast, low-dose corticosteroids
- High dose/prolonged corticosteroids may be a problem
- Consider doing histamine & control PRIOR to SPT on all patients

Cook J Allergy Clin Immunol 1973;51:71-7
Rao KS J Allergy Clin Immunol 1988;82:752-7
Miller J J Allergy Clin Immunol 1989;84:895-99
Slott RIJ Allergy Clin Immunol 1974;554:229-34

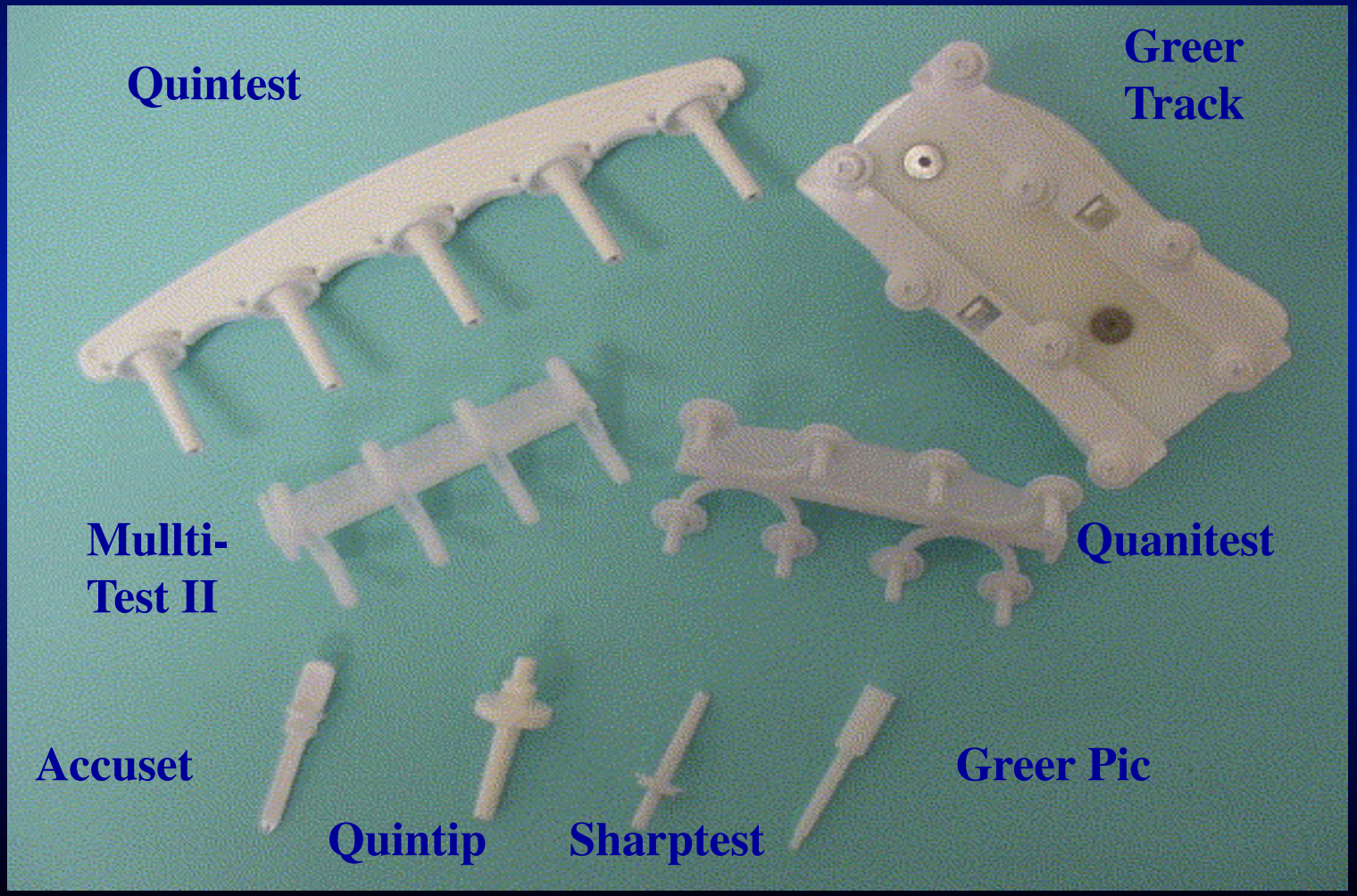
Skin prick testing

- SPT is easy to perform and rarely causes generalized reactions.
- Patients may have positive SPT but no clinical disease. A positive SPT indicates the presence of IgE antibodies against that allergen but does not indicate clinical sensitivity. A correlation between the history and SPT is essential.
- Approximately 3×10^{-6} ml of allergen extract is delivered with each prick
- Prick/puncture tests may be performed in infants as young
- as 1 month

SPT testing solutions with dropper caps

http://www.mayoclinic.com/health/allergy-tests/MM00385

Common SPT devices
Prick & Puncture



Skin Prick Testing Devices

Not all SPT devices are the same

Devices for which a 3 mm wheal would be significant as a positive test (.99 quantile at the neg control site listed)		Devices that require > 3 mm wheal for a positive test (.99 quantile at the neg control site listed)	
Quintest (HS) puncture	0 mm	DuoTip (LincolnO twist	3.5 mm
Smallpox needle *HS) prick	0 mm	Bifurcated needle (ALO) Prick	4.0
DuoTop (Lincoln) ptick	1.5	MultiTest (Lincoln) puncture	4.0
Lancet (HS)	2.0	Bifurcated needle (ALO) puncture	4.5
Lancet (ALK)	3.0	Quick Test (Pantrax)	4.0
DermaPICK II	0	Greer Track (Greer)	3,5

Annals Vol 100, March 2008 Testing, Diagnostic JTF of PP

Characteristics of different regions

Prick Skin Test Reactions by Region of the Back

Location	Histamine	Allergen
Top (n=96)	7.24mm	7.82mm
Mid (n=96)	8.19mm	10.41mm
Bottom (n=96)	8.94mm	11.11mm

Gradient for both significant $p<0.0001$

HS Nelson, et al. JACI 1996;97:596

Allergen drops placed on skin that has been marked with lines/numbers

http://www.mayoclinic.com/health/allergy-tests/MM00385

Positive and negative controls

- Prick Positive control:
  - 1.0 mg/mL histamine base (2.75 mg/mL histamine phosphate aqueous)
  - 1.8 mg/mL histamine base (5 mg/mL histamine phosphate, glycerinated)
  - Need minimum of 2-7 mm flare
- Prick Negative control:
  - 50% glycerinated HSA-saline
- ID Positive control:
  - 0.10 mg/mL histamine base (0.275 mg/mL histamine phosphate aqueous)
- ID negative control:
  - HSA-saline

SPT using Lancet

http://www.mayoclinic.com/health/allergy-tests/MM00385

SPT reading using ruler

Read prick histamine and control at 15 minutes; read allergens at 15-20 minutes

http://www.mayoclinic.com/health/allergy-tests/MM00385

SPT on arm

SPT on back

Intradermal Skin Testing (Upper Arm)

Intradermal Skin Testing (Upper arm)

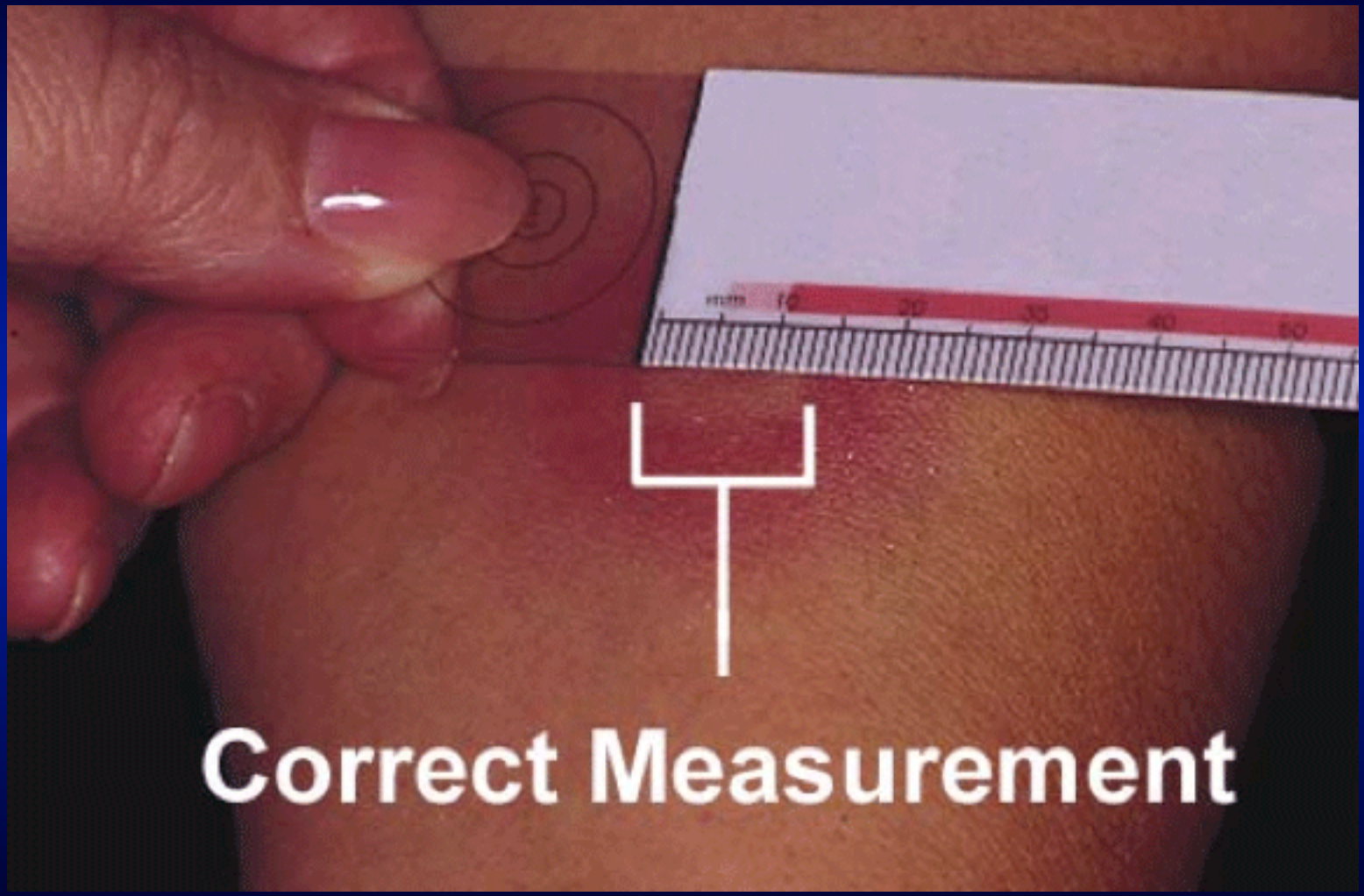
Intradermal skin testing

Deliver 0.02 to 0.05 mL of a diluted (100-1000 fold) prick extract concentration.
This is usually a 1:100 to 1:1000 w/v or 10-100 BAU or AU
Use 26-30 gauge needle.

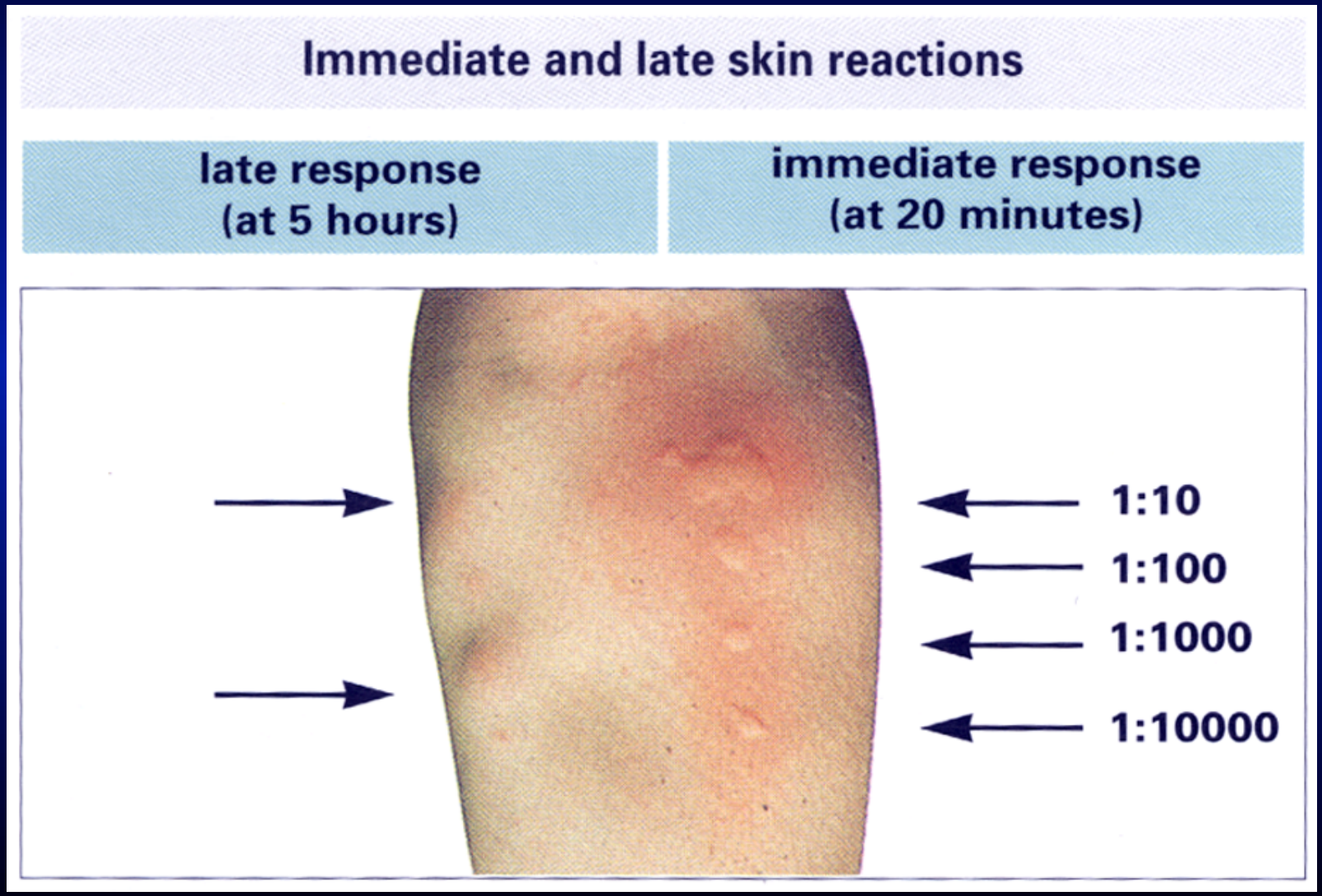
Intradermal Test Reading

Read ID testing to histamine and control at 10 minutes and to allergens at 15 minutes.

Correct skin test measurement



ID End Point Titration



Skin testing elements to record

- Patient demographics
- Technician
- Date and time of day
- Last use of antihistamine (day/time)
- Testing device used
- Location of tests
- Testing concentration (W:V, PNU, AU, BAU)
- Extract manufacturer for each allergen
- Time read after placement (e.g. 15 minutes)

Recording skin test responses

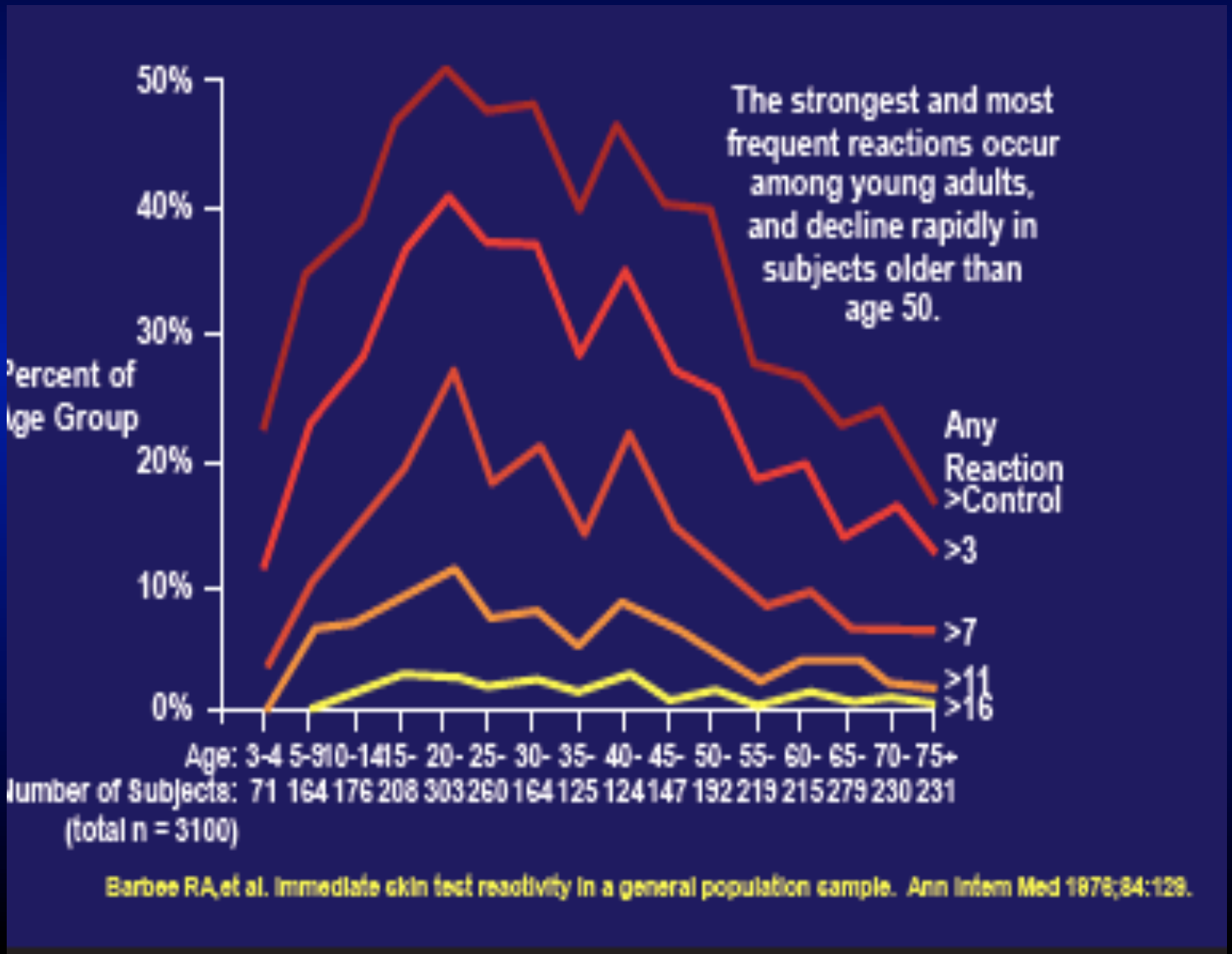
- Useful to report both wheal and flare measurements in **mm** (not a 1+ to 4+ grading)
  - Recommended method is to measure the reaction in mm across the longest diameter and the orthogonal diameter
    - Wheal (e.g. 12 mm x 8 mm)
    - Erythema (e.g. 22 mm X 20)

Inter-individual variation in SPT

Test result	Nurse 1	Nurse 2	Nurse 3	Nurse 4	CV
Negative control	0.1 mm	0.4 mm	0.2 mm	0.2 mm	55.9%
Histamine	11.7 mm	9.7 mm	12.9 mm	14.5 mm	16.6%
Grass	2.1 mm	2.5 mm	4.7 mm	5.2 mm	42.8%
Mugwort	7.7 mm	4.8 mm	7.4 mm	9.1 mm	24.7%
Dog	1.5 mm	1.1 mm	3.0 mm	2.5 mm	43.3%
House dust mite	1.7 mm	2.2 mm	1.6 mm	2.8 mm	26.5%

CV= coefficient of variation, target < 25%

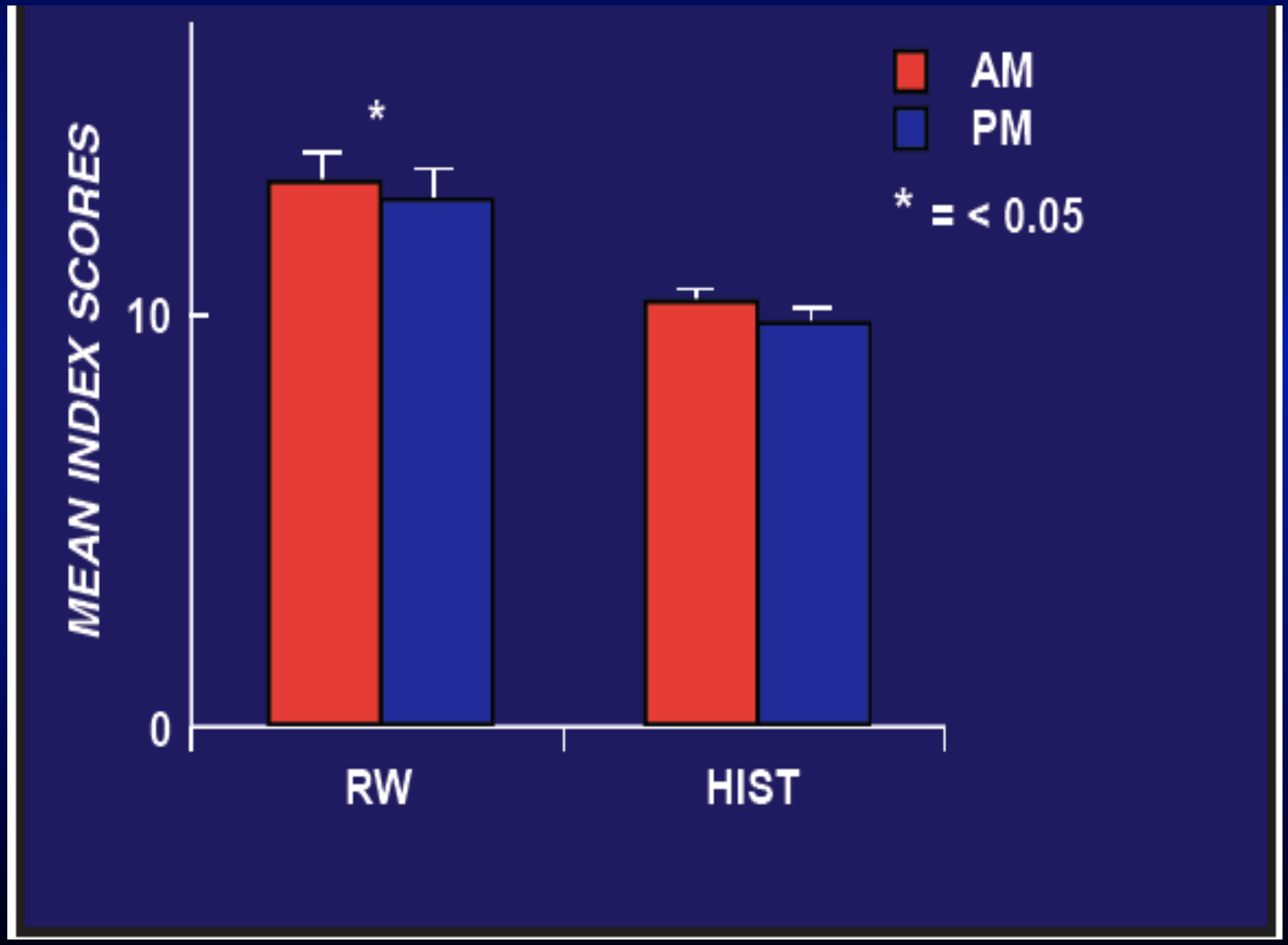
Skin test reactivity based on age



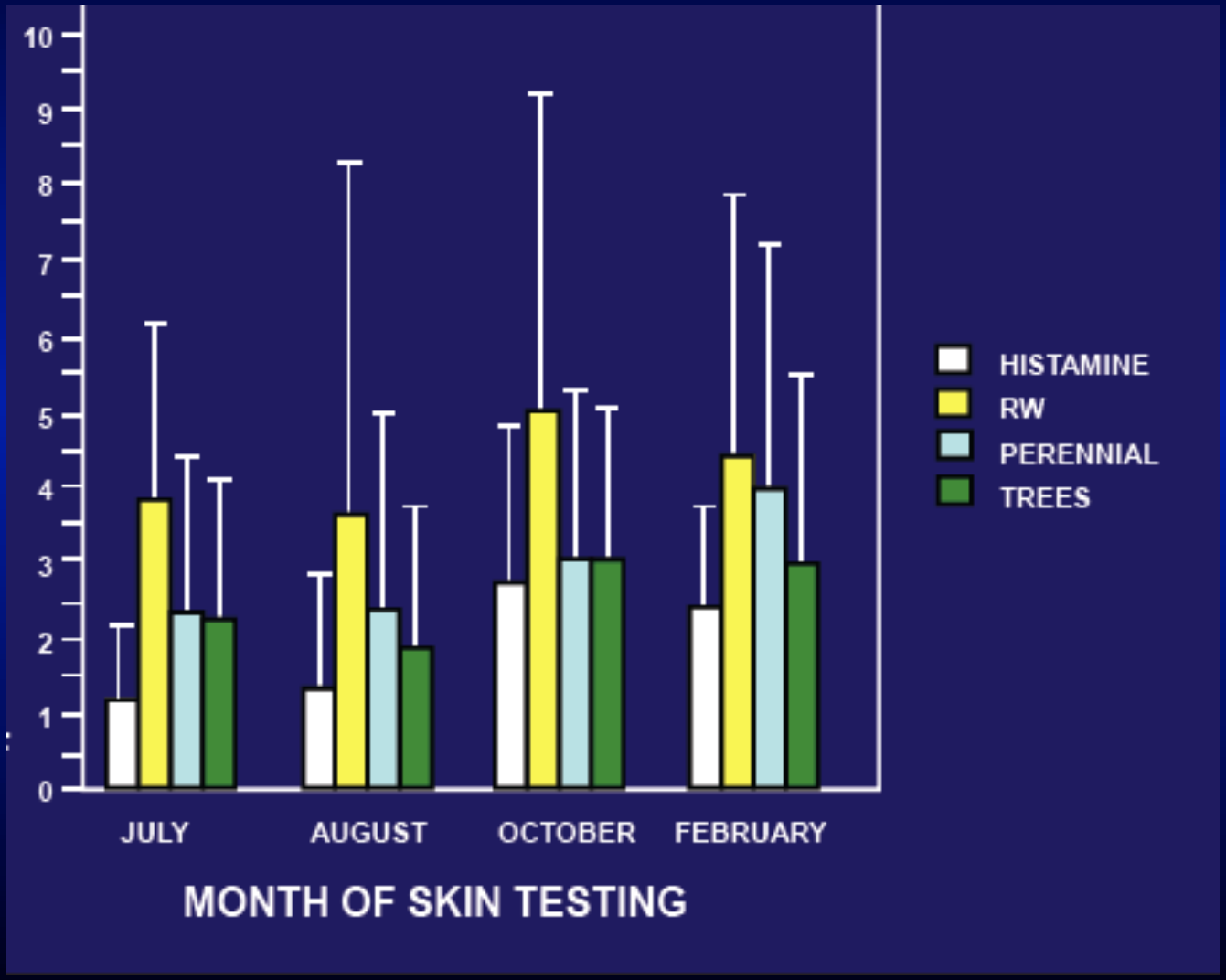
Barbee RA, et al. Immediate skin test reactivity in a general population sample. Ann Intern Med 1976;84:128.

Circadian Skin Reactivity

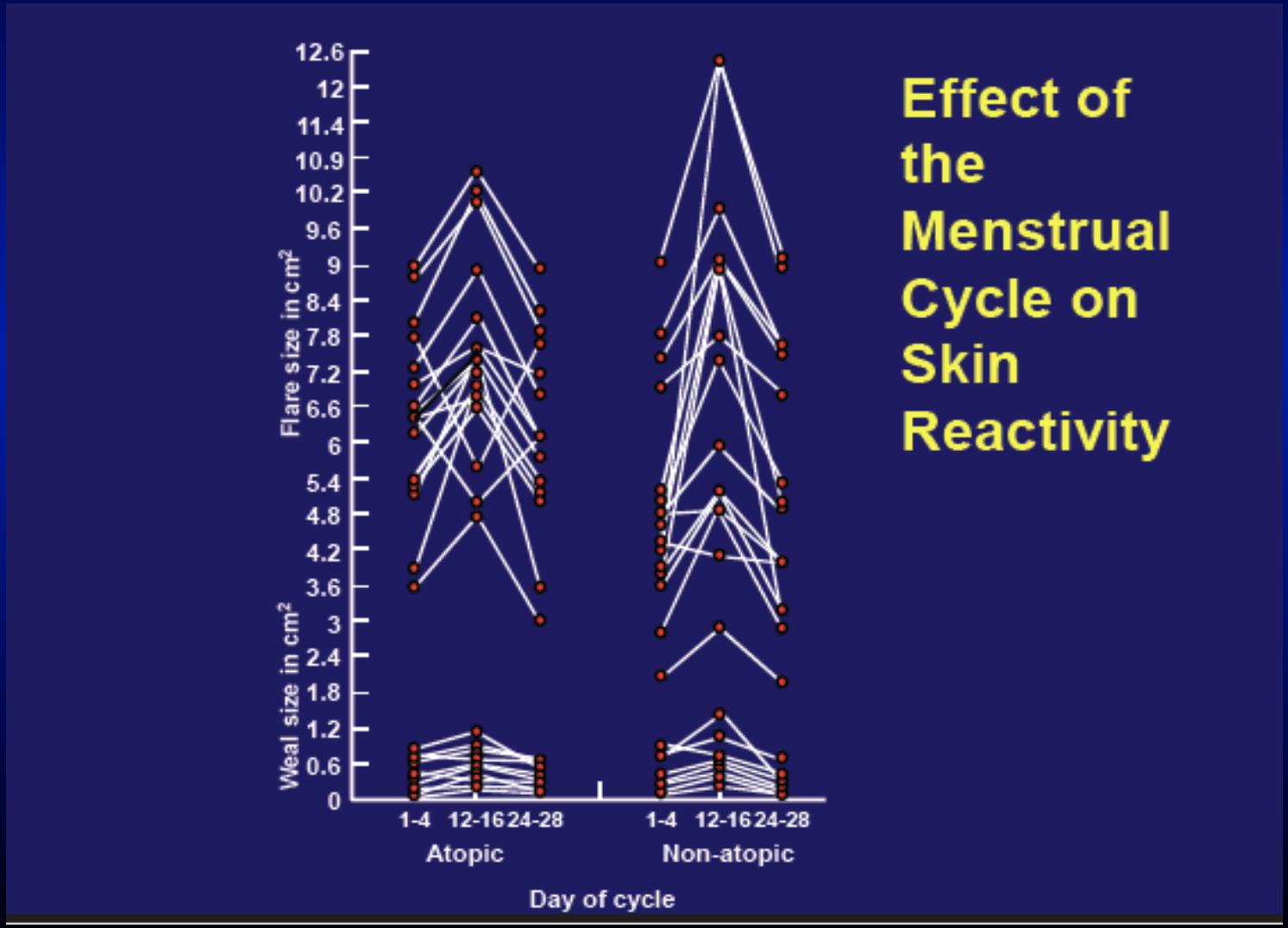
Statistically but not clinically significant



Seasonal variations in SPT



Menstrual Cycle and SPT



SPT based on body region tested ??

Comparison of Prick Skin Test Reactions on the Back and Arm

	Forearm (reaction diameters)	Back	p-
Wheal histamine (n=50)	4.08 mm	3.99 mm	NS
Flare histamine (n=50)	21.67 mm	23.52 mm	0.003
Wheal allergen (n=50)	8.53 mm	11.61 mm	0.001
Flare allergen	31.81 mm	36.78 mm	0.001

HS Nelson, et al. JACI 1996;97:596

SPT vs. ID Testing

Advantages of SPT

- Safer
- More rapid
- Less discomfort to patient
- Technically less demanding
- More specific
- More allergens in one session
- Allergen more stable (50% glycerin)
- Positive and negative tests more easily distinguished
- Steeper dose response curve
- Positive tests correlate better with clinical disease

Advantages of ICT

More sensitive:
(300 to >1000 fold)
More reproducible
More positives

Skin test safety

- Review of surveys of fatal reactions to skin testing between 1959-2001
- 9 deaths associated with skin testing
- 1 death associated with SPT
  - History of unstable asthma with FEV-1 36% 1 week prior
  - Tested to 90 foods
- 8 deaths associated with intradermal testing

Lockey JACI 1987;79:660-77
Reid JACI 1993;92:6-15
Bernstein JACI 2004;113:1129-36

Be Prepared to Treat Anaphylaxis

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allergen avoidance

indicated when possible

pharmacotherapy

safety
effectiveness
easy to be administered

patient

immunotherapy

effectiveness
specialist prescription
may alter the natural course of the disease

patient's education

always indicated