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Professor of Clinical Pharmacology
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Stevens-Johnson/TEN(S)

Clinical Syndromes,
Epidemiology, Genomics,
Diagnosis and Treatment.

Potential Conflicts

- Consultant to pharmaceutical industry related to drug hypersensitivity reactions.
- All therapeutic comments are off-label.

SCAR Clinical Syndromes

Severe Cutaneous Adverse Reactions

- DRESS
 - Drug Reaction with Eosinophilia and Systemic Symptoms
- AGEP
 - Acute Generalized Exanthematous Pustulosis
- SJS/TEN = TENS
 - Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

A NEW ACUTE FEVER ASSOCIATED WITH
STOMATITIS AND OPHTHALMIA
REPORTED IN TWO CASES IN CHILDREN *
A. M. STEVENSON, M.D. C. JOHNSON, M.D.

Stevens and Johnson Syndrome, 1922

TOXIC ERYTHEMA: A SYNDROME OF
AN ERUPTION RESEMBLING SCALDING OF THE SKIN.
ALAN LYELL

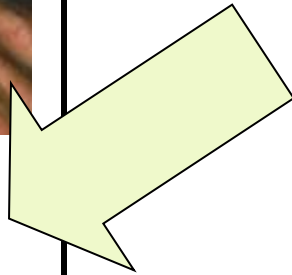
Assistant Physician to the Skin Department, Royal Infirmary, Aberdeen.

Alan Lyell. British Journal of Dermatology, 1956

EM-EMM-SJS/TEN-"TEN": 4+ Diseases



**Erythema
Multiforme**



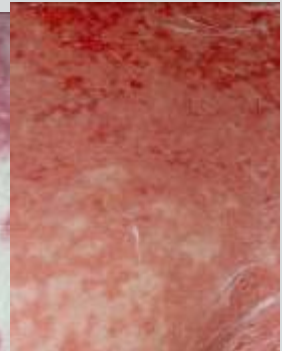
EM Major (& variant)



Other TEN-like

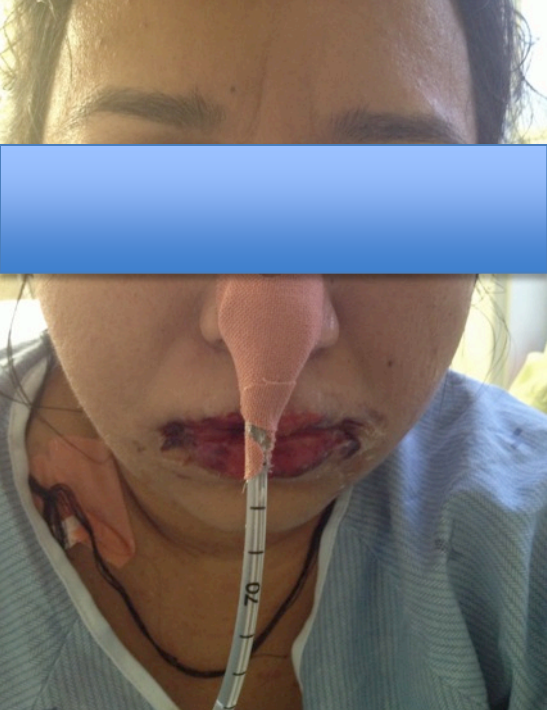


SJS to TEN



A Story

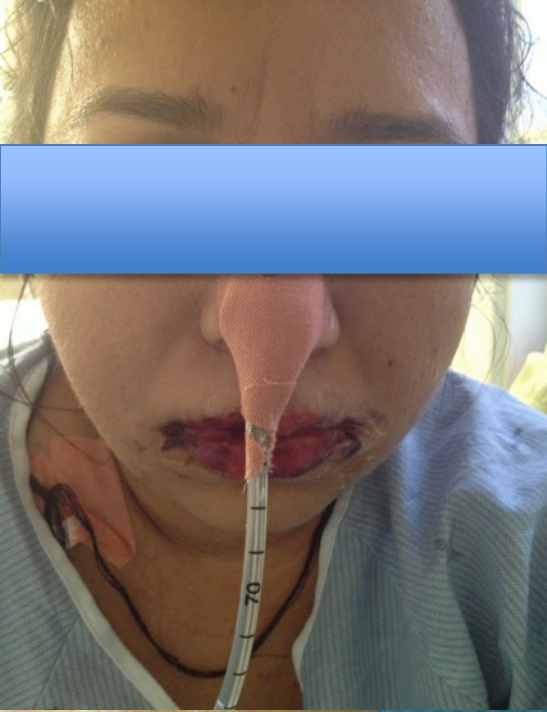
- “Patient with SJS in the Emergency”
 - Caused by Amoxil – taken for a sore throat
- History reveals
 - 39 year old woman
 - Carbamazepine (Tegretol) for 3 weeks
- Does she have SJS? Yes she does!
- What caused it? Carbamazepine?



A 39 y/o Indian female with SJS induced by carbamazepine. Feb 2014

FDA Guidelines

- ▣ **“PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS**
- ▣ **SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE.”**



P-01/01
416 340 3133
UHN-HLA Lab
MAR-07-2014 15:46

Toronto Regional
Histocompatibility Laboratory
67 College Street, Room 301
Toronto, ON M5G 2M1
Phone: 416-340-4995
Fax: 416-340-3133
ASHI #: 06-9-ON-03-1
Directors:
Kathryn Tinckam
Neal denHollander

University Health Network
A Division of Mount Sinai Hospital

MRN: [REDACTED]
ABO Code: [REDACTED]
Category: Other
Physician: [REDACTED]
Hospital: Sunnybrook Hospital

Histocompatibility Laboratory Report

HLA Typing Results

Relation	Haplo A*	B*	Bw	C*	DRB1*	DRB345*	DQA1*	DQB1*	DPA1*	DPB1*	Test Date
Self		15:02(75) 40:06(61)									Mar/07/2014 Feb/27/2014

Local typing done by PCR-SSO and/or PCR-SSP.
HLA typed elsewhere when indicated by: ‡
ABO testing not performed in the HLA Lab. All ABO results should be verified by ordering physician.

Comments

B*15:02 is present.
Ordering physician: Dr. Neal Shear

Comments

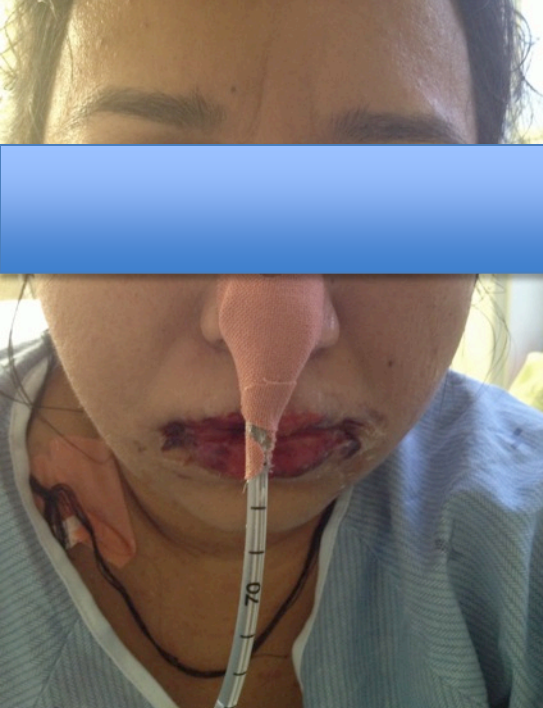
B*15:02 is present.

Created by: Amanda Nowry
Reviewed by: Alice van Oosterwijk, Supervisor
Electronically Verified By: Alice van Oosterwijk, Supervisor

Date: Mar/07/2014
Date: Mar/07/2014
Date: Mar/07/2014

Printed Date: Mar/07/2014 15:42

A 39 y/o Indian female with SJS induced by carbamazepine. Feb 2014



P-01/01
416 940 3130

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MRN: [REDACTED]
ABO Code: [REDACTED]
Category: Other
Physician:
Hospital: Sunnybrook Hospital

TOTAL: P. 01

Histocompatibility Laboratory Report

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Self			15:02(79) 40:06(61)									Mar/07/2014 Feb/27/2014

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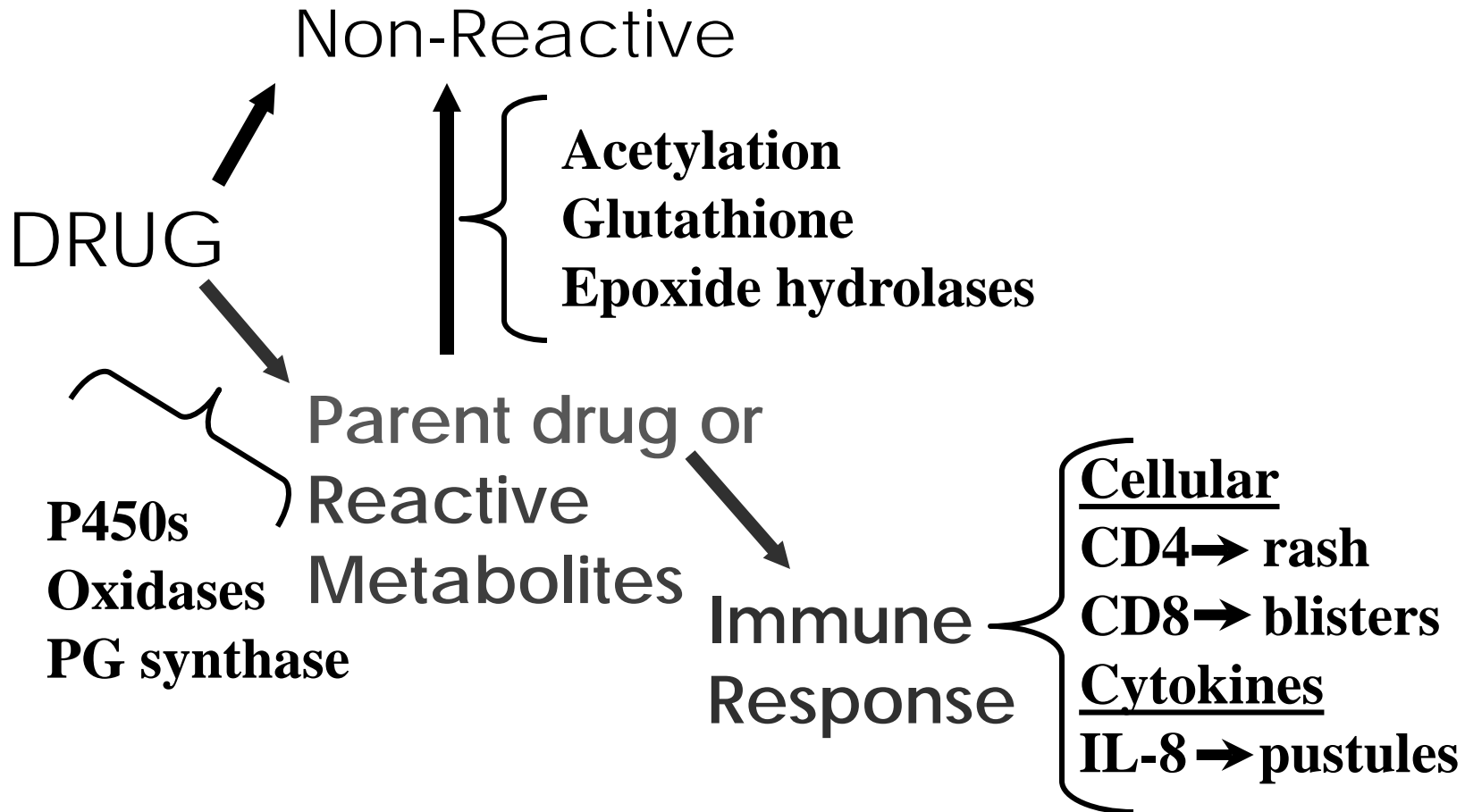
Page 1 of 1

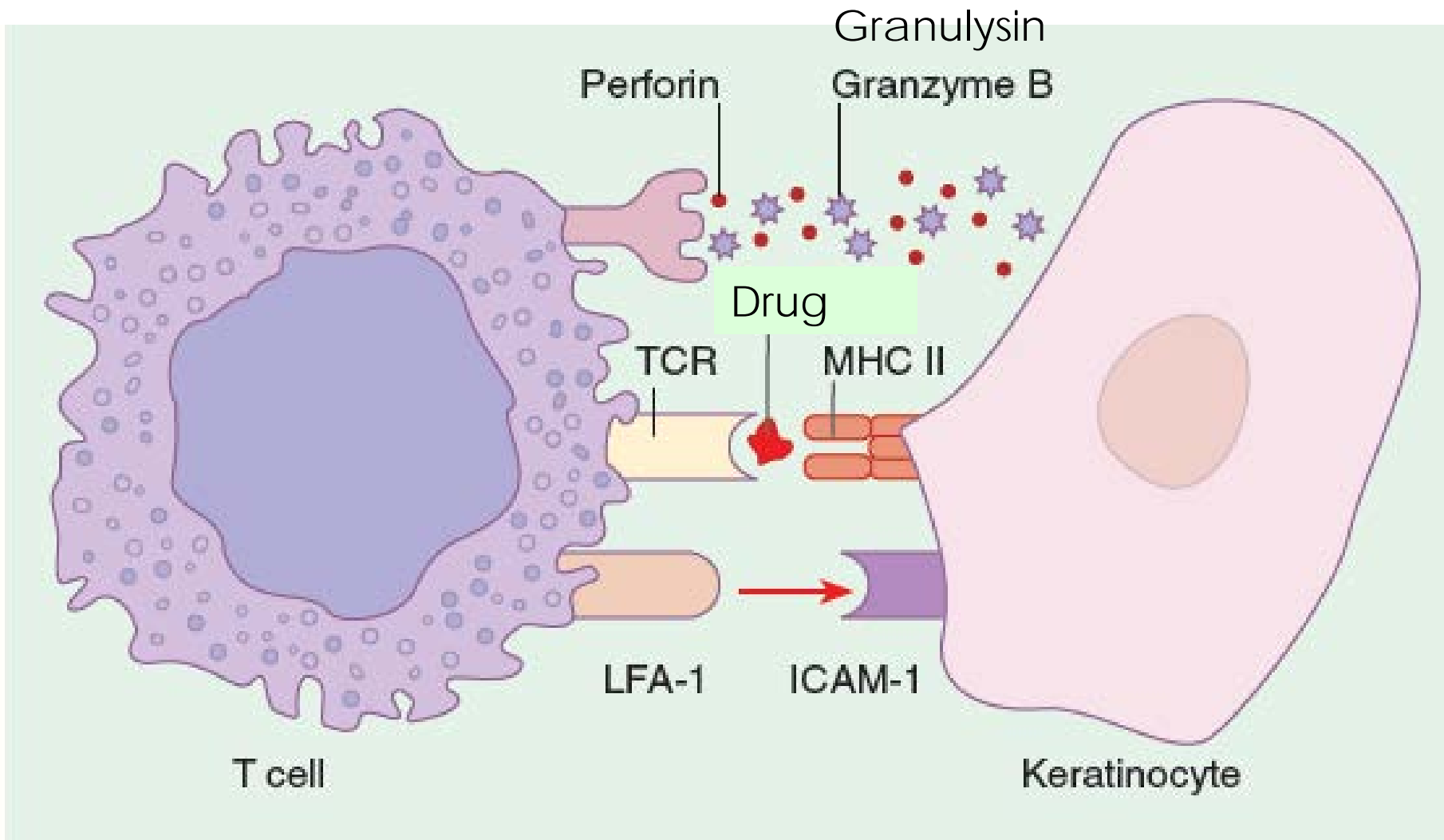
A 39 y/o Indian female with SJS Induced by carbamazepine. Feb 2014

The importance of positive HLA test:

- Support diagnosis
- Confirm the suspected offending drug
- Valuable for familial genetic consultation

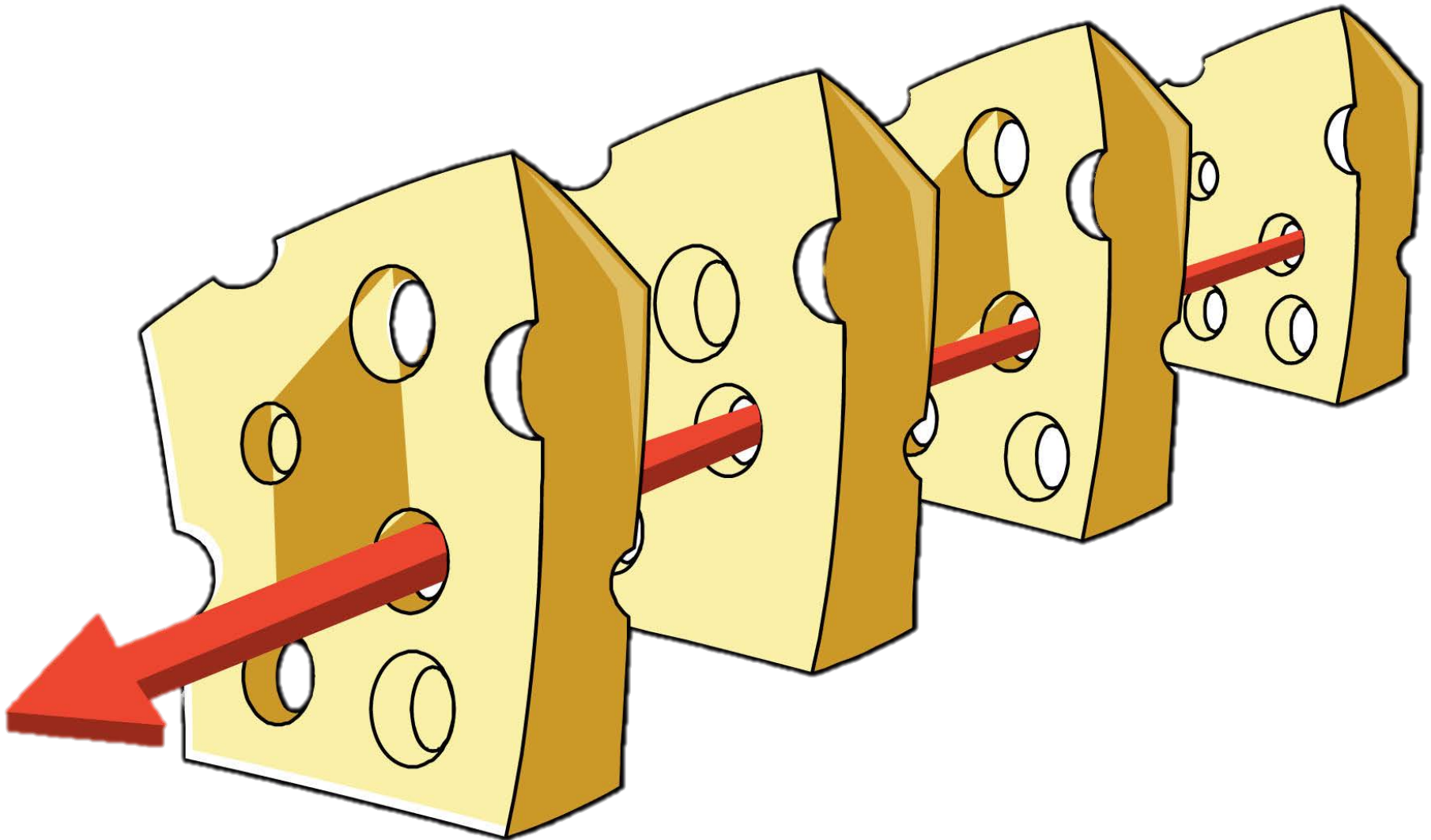
Pathophysiology of Immune-Mediated Drug Reactions





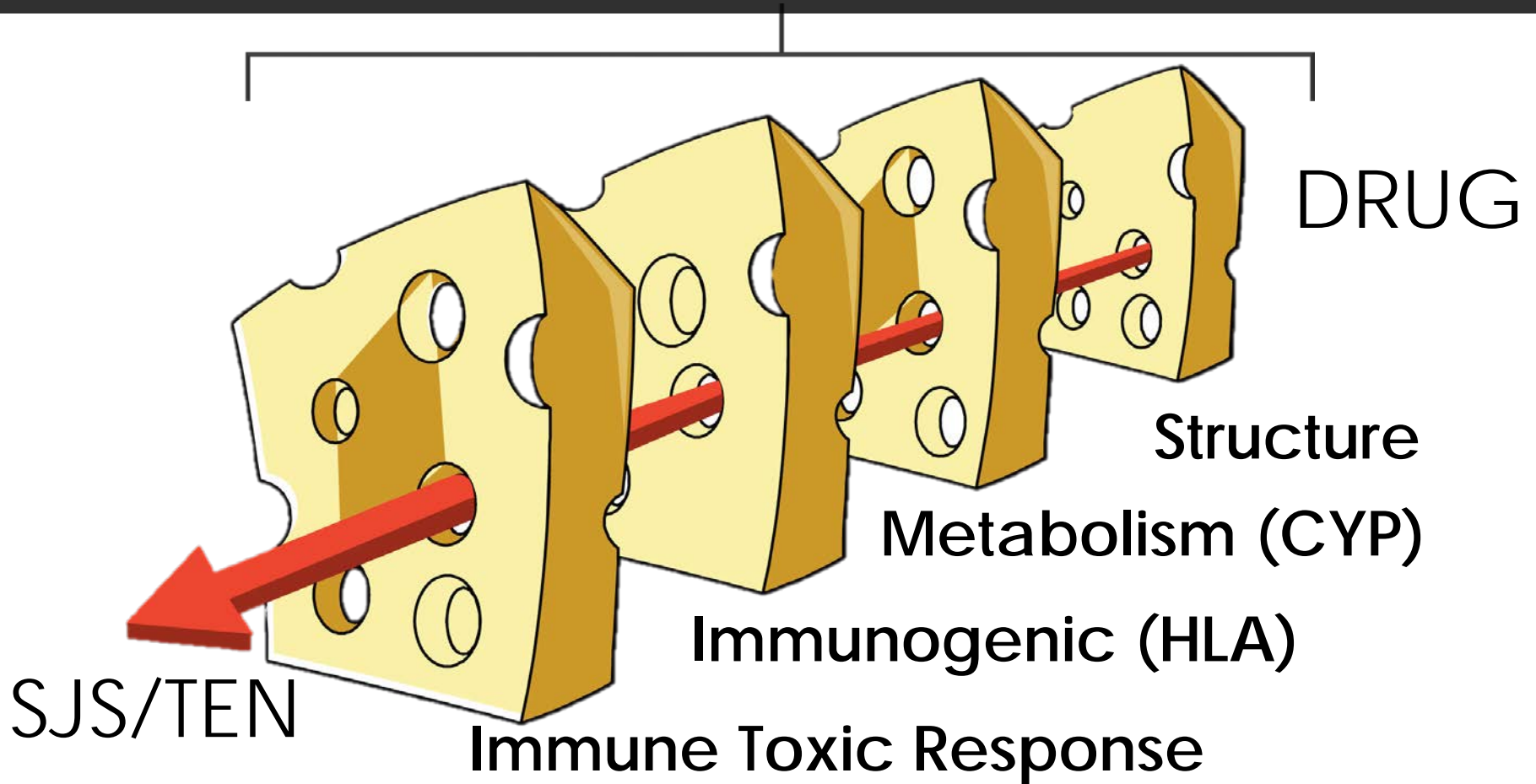
Drug fits in HLA groove – SJS/TEN

J.T. Reason: Swiss Cheese Model



Model of a Drug Reaction

Putative Risk Factors



Her Brother

- He has been taking carbamazepine for 3 years
- He has had no problems with it.
- We tested him for HLA-B*15:02
- Guess what?

Her Brother

- He has been taking carbamazepine for 3 years
- He has had no problems with it.
- We tested him for HLA-B*15:02
- Guess what?
- He too was HLA-B*15:02 Positive

Epidemiology

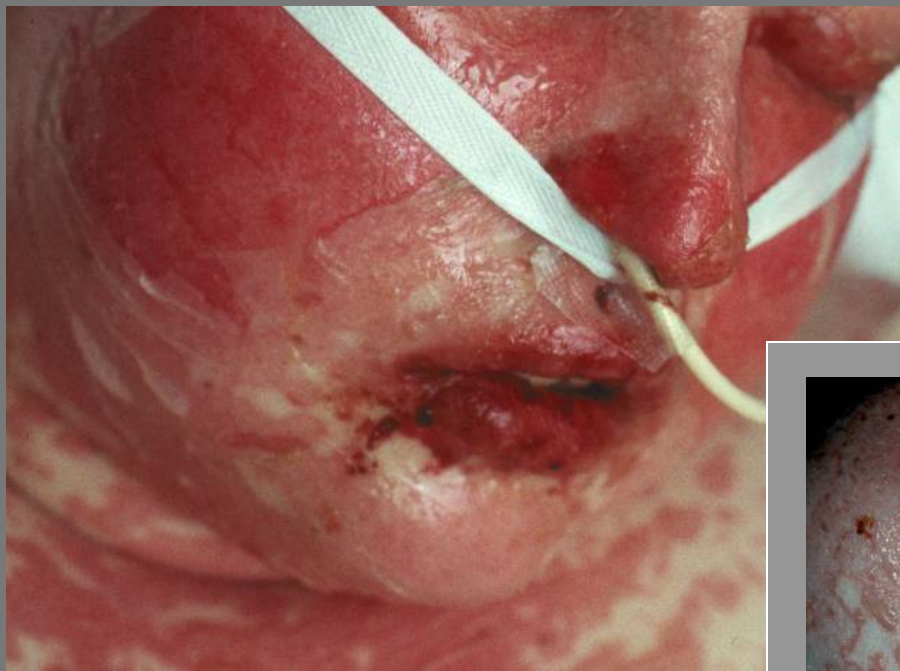
- Dodiuk-Gad, Laws, Shear
- Seminars in Cutaneous Medicine and Surgery
- 2014
- "SJS/TEN is rare (1 per million population)"

Genomics

TABLE I. Pharmacogenomics of HLA-associated drug hypersensitivity and related drug-induced syndromes

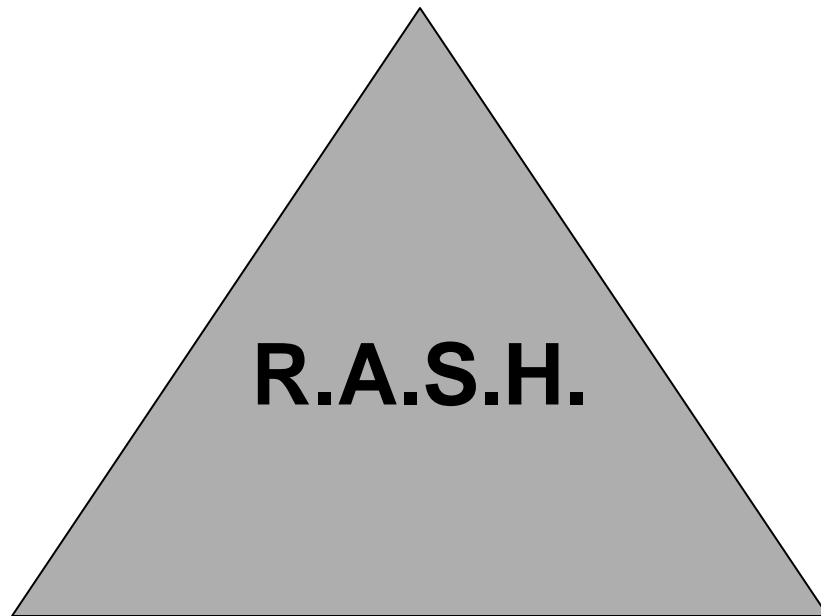
Syndrome and drug	HLA Alleles	Populations	Year first described
SJS-TEN (SCAR)			
Allopurinol	B*58:01	Han Chinese, Thai, European, Italian, Korean, Portuguese	2005
CBZ	B*15:02	Han Chinese, Thai, Malaysian, Indian	2004
	B*15:11	Korean, Japanese	2010
	B*15:18, B*59:01, and Cw*07:04	Japanese	2010
	A*31:01	Japanese, northern European, Korean	2011
Oxcarbazepine	B*15:02	Han Chinese	2010
Lamotrigine	B*15:02, positive	Han Chinese	2010
	B*15:02, no association found	Han Chinese	2010
Nevirapine	C*04:01	Malawian	2013
Phenytoin	B*15:02; B*13:01, Cw*08:01, and DRB1*16:02	Han Chinese	2007
Phenobarbital	B*51:01	Japanese	2013
Sulfamethoxazole	B*38	European	2008
Methazolamide	B*59, B*59:01, Cw*01:02 alleles, and B*59:01-Cw*01:02-A*24:02 haplotype	Japanese, Korean, and Japanese	1997, 2011
Sulfonamides	A*29, B*12, and DR*7	European	1987
Oxicam	B*73	European	2008
	A*2,B*12	European	1987
Strontium ranelate	Under investigation in postmarketing period		2009
Zonisamide	A*02:07	Japanese	2013

Diagnosis of TENS



Shear's Diagnostic Triangle

APPEARANCE



SYSTEMIC (Fever)

HISTOLOGY

Remember: Apppearance, Systemic, Histology

Special Article

Clinical Classification of Cases of Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, and Erythema Multiforme

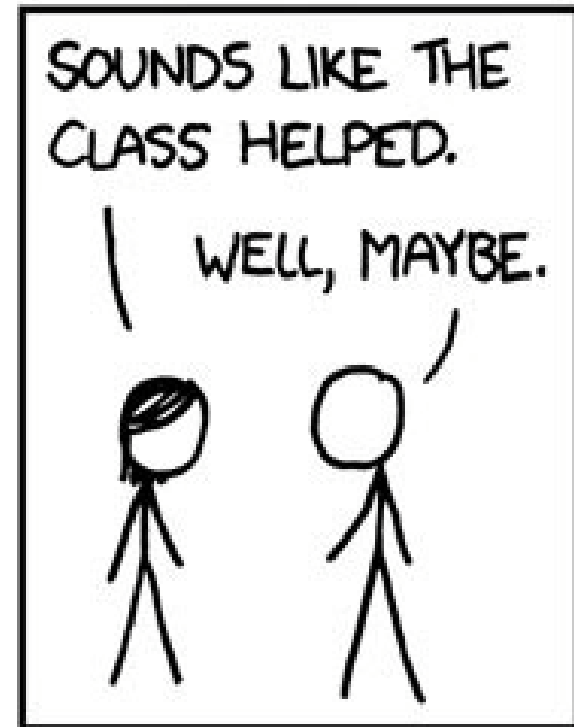
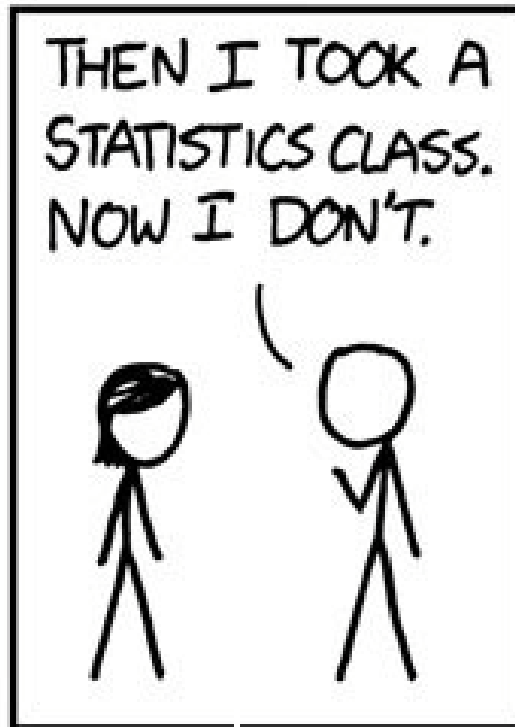
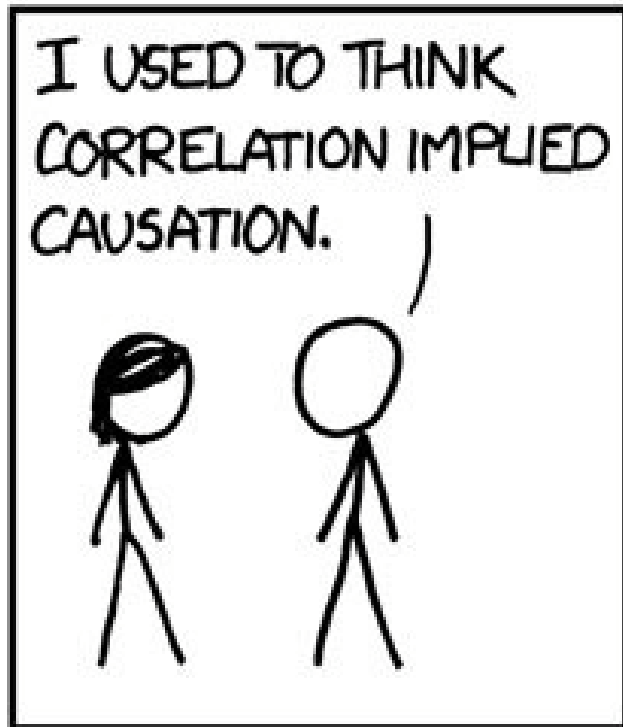
Sylvie Bastuji-Garin, MD; Berthold Rzany, MD; Robert S. Stern, MD;
Neil H. Shear, MD, FRCPC; Luigi Naldi, MD; Jean-Claude Roujeau, MD

Proposed Classification of Cases in the Spectrum of Severe Bullous EM*					
Classification	Bullous EM	SJS	Overlap SJS-TEN	TEN	
				With Spots	Without Spots
Detachment	<10%	<10%	10%-30%	>30%	>10%
Typical targets	Yes
Atypical targets	Raised	Flat	Flat	Flat	...
Spots	...	Yes	Yes	Yes	...

*EM indicates erythema multiforme; SJS, Stevens-Johnson syndrome; and TEN, toxic epidermal necrolysis.

Bastuji-Garin et al.
Arch Dermatol. 1993

Causality Assessment (via XKCD)



Treatment

- Hugely variable
- Burn Unit w/ support
- *Survey of Canadian & USA units*
 - Corticosteroids
 - Cyclosporine
 - Anti-TNF therapy

Treatment part 2

- Eyes
 - Amniotic membrane
- Genitals
 - Examination and daily care
- Post-traumatic syndromes in survivors

We can do better

- ▣ Patients that should be screened are not being screened
- ▣ Better communication must follow the advance in science
- ▣ Care guidelines during and post TEN are needed

Partnering for Success

Pure Public

FDA

Pure Private

NIH



IND.



Research Applications



UNI.

Science

Safety

Efficacy

iSCAR at WCD – Vancouver 2015

- Tuesday, June 8, 2015
- World Congress of Dermatology
- <http://sunnybrook.ca/iscar2015>