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Physiology & False Memories: The Role of the Mental Health Professional



J. Douglas Bremner, MD Emory University, Atlanta, Georgia

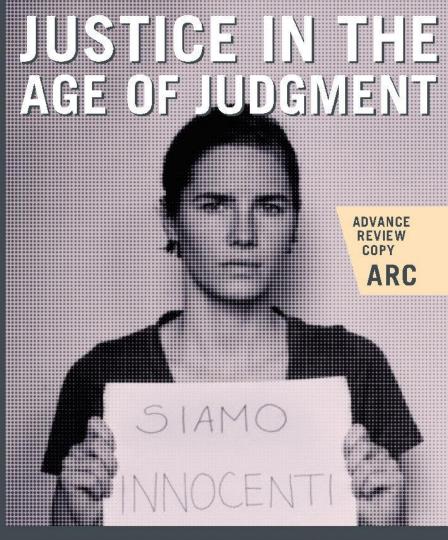
www.dougbremner.com





ANNE BREMNER, JD, is a veteran trial attorney and one of the nation's most tecognized legal analysts. Her practice emphasizes civil rights, catastrophic loss, defense, and criminal law. In her decades of practice, she has been lead counsel for many highly publicized court cases. Anne is a regular contributing legal analyst on television, appearing regularly on CNN, Fox, CBS, NBC, MSNBC, the BBC, Court TV and others. She has been voted one of the best lawyers in Seattle and one of Seattle's Top 25 most influential people. She is a Stanford graduate and has a perfect AVVO rating as an attorney. She lives in Seattle, Washington.

Doug Bremner, MD, is a psychiatrist, researcher, writer, and professor at Emory University in Atlanta, Georgia. Dr. Bremner is a world leader in research in the field of posttraumatic stress disorder (PTSD) and memory, including studies related to false memories with relevance to coerced testimony. He has served as an expert witness in litigation related to PTSD and drug safety and has often appeared on CNN as an expert analyst. He has written over 400 research papers and several best-selling books including Does Stress Damage the Brain? and Before You Take That Pill: Risks and Side I ffects You Won't Find on the Label cf Commonly Prescribed Medications, Vitamins and Supplements. Dr. Bremner lives in Atlanta, Georgia.



ANNE BREMNER, JD

AND DOUG BREMNER, MD

BREMNER

Role of Mental Health in Criminal Judicial Proceedings

- Provide context and interpretation of forensic findings for jury
- Protect accused against erroneous selfincrimination
- Use science & medicine to establish causality, determine time lines, establish guilt and innocence, protect patients

Media Sensalization of High Profile Crimes

- Photogenic protagonists
- Incites touchstone issues of the times
- Voyeuristic aspects
- Sells newspapers or goes viral online
- Creation of online communities parallel public nature of punishment in prior eras

Role of Bias in Judicial Proceedings

- People tend to make up their mind early
- Confirmation bias: Looking for information to support original conclusions
- Recency bias: Use of information most fresh in your mind
- Jurors receive instruction to remove bias

Journal of Personality and Social Psychology 1975, Vol. 32, No. 5, 880-892

Perseverance in Self-Perception and Social Perception: Biased Attributional Processes in the Debriefing Paradigm

Lee Ross, Mark R. Lepper, and Michael Hubbard Stanford University

Two experiments demonstrated that self-perceptions and social perceptions may persevere after the initial basis for such perceptions has been completely discredited. In both studies subjects first received false feedback, indicating that they had either succeeded or failed on a novel discrimination task and then were thoroughly debriefed concerning the predetermined and random nature of this outcome manipulation. In Experiment 2, both the initial outcome manipulation and subsequent debriefing were watched and overheard by observers. Both actors and observers showed substantial perseverance of initial

- Students told they were in an experiment in decision making
- Given suicide notes and rates them as true or fake
- Divided into successful, average, or failure groups

- Given misleading information about success
- (told they got it wrong when it was right, etc)
- Students kept scorecard on their performance
- Debriefed about deception later
- Told it was an experiment on "the effects of success and failure on physiological measures"

Perseverance in Self-Perception and Social Perception

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found the task interesting, that they believed it to be a test of ability, and yet accepted extreme outcomes as highly plausible.

Delay manipulation. After the last identification trial, the experimenter collected the cards, leaving the subject's answer sheet on the table. He then explained that it would be necessary to obtain further "baseline" physiological responses "for comparison purposes" and that it might be necessary for subjects to wait "anywhere from 5 minutes to half an hour in order to obtain a stable baseline pattern." The experimenter indicated that he would be monitoring the subject's readings from another room and that he would return as soon as possible. The subject was then left alone for a period of either 5 (short delay) or 25 (long delay) minutes, after which the experimentar returned and removed the

TABLE 1
Actors' Postdebriefing Perceptions of Their Performance and Ability, Experiment 1

Item	Success	Average	Failure	I for linear trend
Estimated initial no. correct ^a	17.05	15.85	12.75	25.30**
Estimate for average student ⁿ	15.50	15.82	14.20	2.82
Predicted future no. correct ^a	16.67	15.72	13.48	10.96*
Rated ability at task ^b	5.28	4.92	3.90	14.82**
Rated abilities at related skills ^b	4.78	4.45	4.20	8.41*

Students in the "failure" group rated their performance worse and downgraded their skills even when told about the experiment

- Second study had students and observers
- Both rated the "failure" group as worse even after told the nature of the experiment
- Second instruction told specifically about study of perseverance of perception
- Observers continue to downgrade "failure" group

Item	No debriefing			Outcome debriefing			Process debriefing					
	Success	Failure	t	Success	Failure	t	Success	Failure	t			
Actors												
Estimated initial no. correct Estimate for	22.75	9,50	11.84***	18.33	12.83	5.91****	16.50	15.17	<1			
average student Predicted future	21.17	12.00	7.49****	17.17	13.58	4.65****	16.08	16.25	<1			
no. correct	21.08	11.42	6.21****	18.33	14.25	4.23****	16.33	16.08	<1			
Rated ability at task	5.25	2.58	4.57***	5.00	3.83	2.65**	4.75	3.83	1.81*			
Rated abilities at related skills	4.22	4.53	<1	4.69	4.53	<1	4.56	4.42	<1			
Observers												
Estimated initial no. correct Estimate for	23.83	10.08	24.21****	19.00	12.42	4.43****	16.92	12.00	3.02***			
average student	20.17	11.75	9.14****	18.25	13.83	3.61***	15.67	13.83	1.41			
Predicted future no. correct Rated ability	22.75	12.08	14.53****	19.08	14.50	2.68**	16.75	14.58	1.36			

Observers continue to rate students in the "failure" group as worse even when briefed on the true purpose of the experiment

- Early information biases perception
- First impression remains even when advised of the "rigged" nature of the experiment
- Effect stronger for outside observers
- Relevance to juries and judicial proceedings
- Relevance to eyewitness identification

Media Sensalization of Amanda Knox Case

- Attractive young couple and victim
- Latent tensions between England and US, Europe and US fault lines
- Voyeuristic- sex and sacrifice rituals
- Sold in the tabloids and created multiple online forums that became their own communities, witnessing and commenting



Photo of chemical used for detection of small amounts of blood leaked to press with information that Knox blood found in bathroom

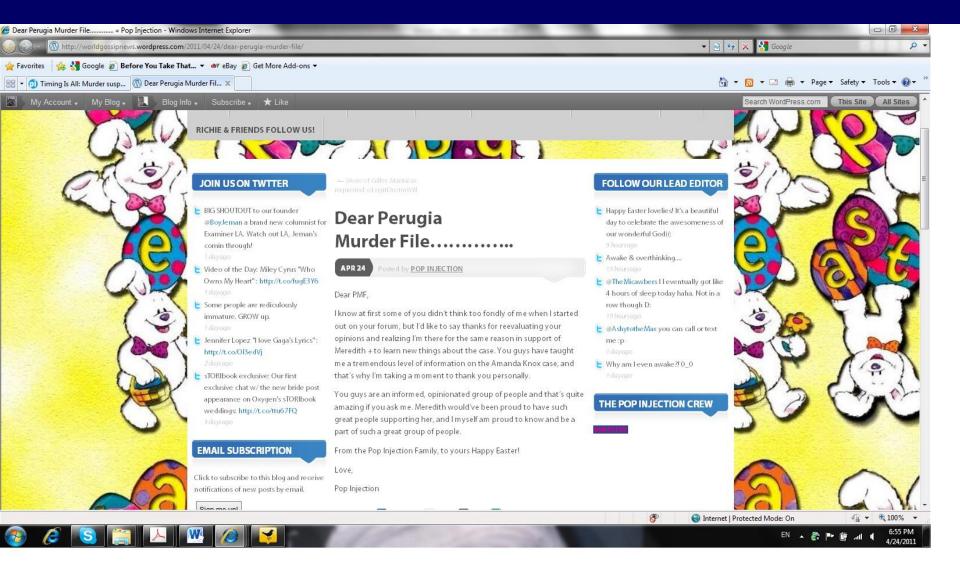


- Proliferation of online frauds, fakes, and attention seekers
- Derik Ritchie, fake person who created a fake gay teenager online
- Created fake boyfriend who killed himself because of bullying
- As media approached he vanished



- Moved on to Amanda Knox case with new persona
- Wrote fake articles about popularity of his web site
- Claimed Knox supporters were blocking him from going to the library
- Got attention from PMF

Darik Ritchie and the Perugia Murder File



The Amanda Knox PR Super Tanker Pulls into Port

Bruce Fisher-TM





Point Blank!



Journalists "abroad" in Italy Andrea Vogt and Barbie Nadeau pick bones of Amanda Knox case.



- Patrizia Stefanoni with the Perugia
 Polizia Scientifica
- ran samples below limit of detection
- returned to crime scene weeks later
- did not maintain nor contaminated lab



Rogues gallery of the trial Showtime!



Your tweet was over 14



BLNadeau BLNadeau

Baby killer feeling better. His lawyer says he will co



BLNadeau BLNadeau

Court still in recess. Jury deciding whether convicts



Court has been in session for two hours and nothin



Baby killer feeling ill. Can't come back to stand.



Amanda wearing a white skirt and navy blouse.



Trial in recess again, second time this morning. Witnesses don't have to answer questions.

Barbie tweets in real time



Mafioso whose brother supposedly killed kercher is on the stand. He looks about 12 years old.



the convicted child killer opted out of testifying on amanda knox's behalf once judge asked if he knew he had to tell truth.





looked like a 12 year old

Maresca Il prosecutor

"Pasta time!

Handwriting expert claims "proof" of guilt based on handwriting "evidence".

Later found to have fabricated psychology degree





Fox news and Anne Coulter chime in "she just looks guilty!"

- Don Murphy, producer of "Transformers" movies
- ODO cult maker, dreamed of making Manson film
- Harrassed online movie fans
- punched out by Quentin Tarentino
- Obsessed with Knox case
- Tried to get Wikipedia page deleted
- Planned movie about DB/AB
- from standpoint of 'guilt'







Key Issues in Case

- Establish time of death
- Medical experts gave opinions not supported by medical science – e.g. stomach emptying
- Lack of sufficient training, ability or expertise

 e.g. lab technician adjusting range of
 detection for DNA, contaminated collection
- Neutral process for collecting and evaluating evidence was violated

Key Issues in Case

- Illegal interrogation with coercion and false confession
- Investigator pre-conceived notions with confirmation bias
- Inappropriate leaks to press poisoned fair process of justice



Giuliano Mignini

Perugia prosecutor with pre-conceived notions about facts of the case, belief in Satanic cults and Masonic conspiracies.

Gastric Emptying Times & Time of Death

- Finite period of time for food to transit stomach to small intestine
- 2-3 hours to pass through stomach
- 82 minutes median time to arrive at duodenum (65-102)
- Transit stops at time of death, stomach contents used to establish time of death

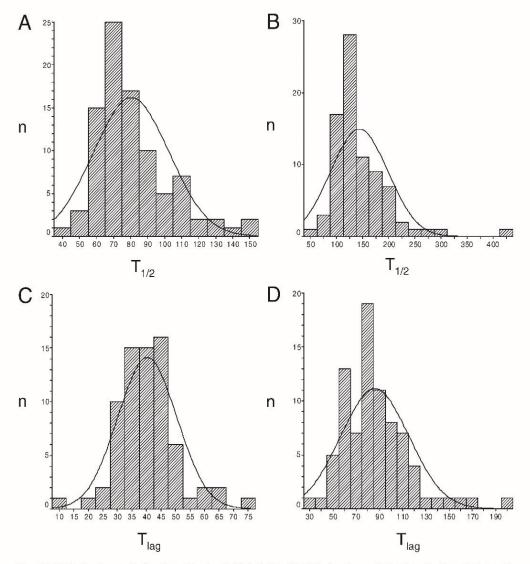


Figure 1 Distribution of grouped half gastric emptying time ($T_{1:2}$) for (a) fluid and (b) solid test meals, as well as lag phase (T_{legr} time of fastest gastric emptying) for (c) fluid and (d) solid test meals.

Gastric Emptying Times & Time of Death

Hellmig et al 2006 J Gastroenterol & Hepatol

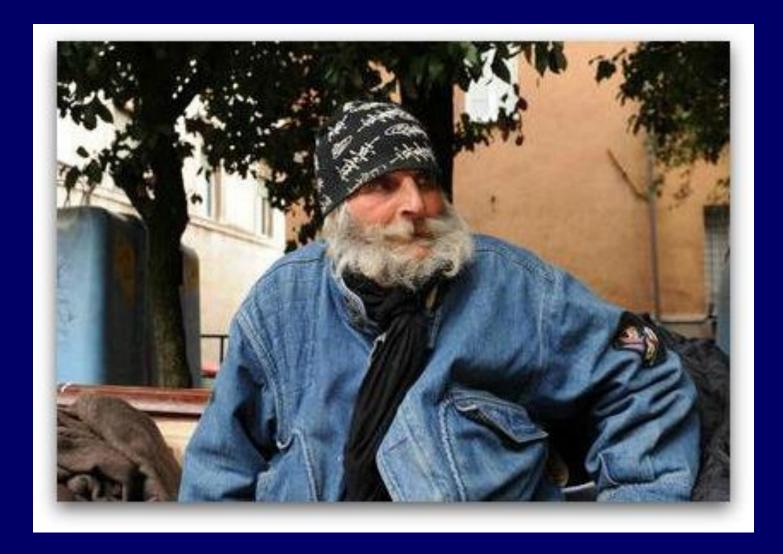
Gastric Emptying Times & Time of Death

- Meredith Kercher ate with three English friends at 6 pm (6:30 pm at latest)
- Confirmed by fact they watched 123 minute movie, arrived home at 9 pm.
- Ten minute walk home, phone call dropped at 8:56 – narrow streets
- Captured on CCTV at 8:51 pm



Gastric Emptying Times & Time of Death

- Meredith Kercher had no contents in duodenum at time of death
- Time of death could not be beyond 9 pm
- Prosecution based case on 11 pm time of death based on witness testimony
- Medical experts falsely claimed wide possibility of transit times



Antonio Curatolo

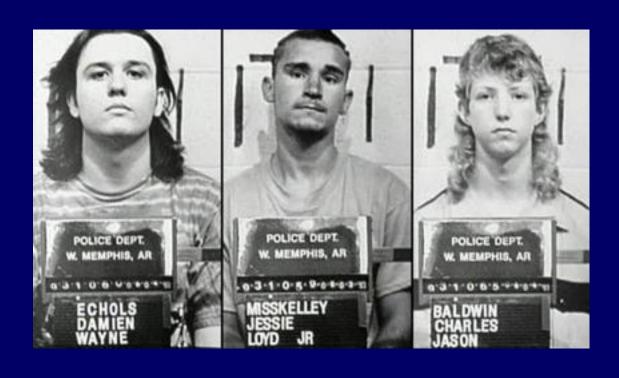
Homeless heroin-addicted resident of Perugia, Italy placed suspects in local square at 11 pm, confused days



Amanda Knox & Perugia Police

- Perugia police used coercive and illegal interrogation tactics
- Increased likelihood of false confessions
- One quarter of convicted exonerated by DNA shown to have made false confession
- West Memphis Three

The West Memphis Three

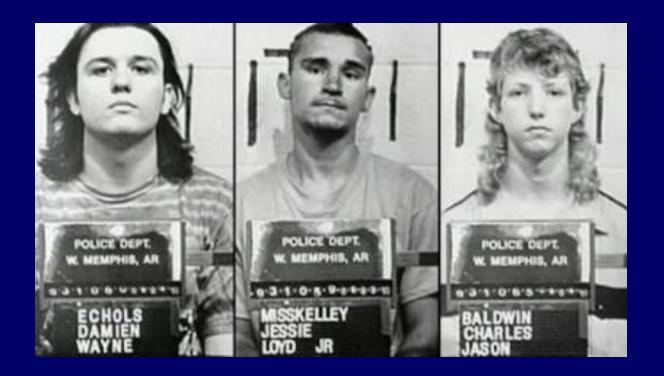


The West Memphis Three

- Three boys found dead, hog tied and possibly sexually abused in West Memphis, Arkansas
- Coerced confession leads to arrest of three local teenagers
- Police and prosecutors leak to media about satanic cult sacrifices
- Boys spend 18 years in prison

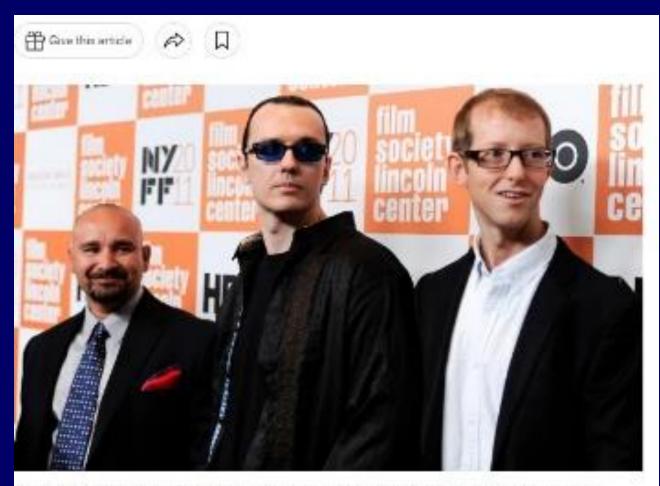
The West Memphis Three

- Child witness has probable false recall of event
- Main witness admits to attempt to avert prosecution
- Taped interviews suppressed
- Prosecutor and police misconduct



- West Memphis Three
- Accused of murder of young boy
- Rumors of satanic cult worship
- Officers under pressure to close case
- Illegal interrogation with forced confession

The West Memphis Three



Jessie Misskelley, left, Damien Echols, center, and Jason Baldwin in October in New York. Evan Agustini/Associated Press

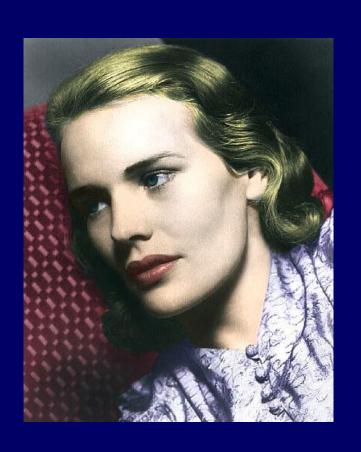


- West Memphis Three
- One year out of release from prison
- Eventually exonerated
- Subject of film in US

Tragic Tale of Frances Farmer

- Born in Seattle, WA
- Starred in Hollywood as an actress opposite Bing Crosby in Rhythm on the Range
- Won an essay contest in 1931 for "God is Dead"
- Railroaded by parents, judges, and psychiatrists

Tragic Tale of Frances Farmer



- Pulled over for driving with high beams on
- Dragged into court
- Subject of media storm
- Committed by psychiatrist

FRANCES FARMER TO GET HEARING

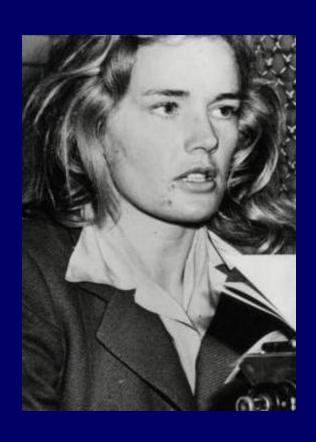
HOLLYWOOD, Jan. 15. (UP)—A complaint was filed in superior court today asking a hearing to determine the sanity of Frances Farmer, blond screen actress jailed yesterday after a 24-hour spree.

Dr. Thomas Leonard, a psychia- of trist, filed the complaint, and Miss a Farmer was ordered removed immediately to general hospital pend- t



Western Washington State Mental Hospital c 1931 Home for Frances Farmer for many years

Tragic Tale of Frances Farmer



- Put in custody of mother
- Placed in mental hospital
- Likely victim of psychiatric abuse
- Died at age 56

Nirvana: "Frances Farmer will Have Her Revenge on Seattle

In her false witness,

Hope you're still with us,

To see if they float or drown.

Our favorite patient,

A display of patience,

Disease-covered Puget Sound.

She'll come back as fire

To burn all the liars,

Leave a blanket of ash on the ground.

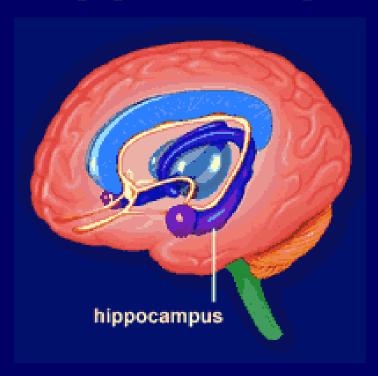
Interrogation of Amanda Knox

- Lengthy interrogation without access to legal counsel or recording, misrepresentations
- Interpreter aided interrogators, not neutral
- 12 police rotating for all night interrogation
- "Imagine" Patrick Lumumba at scene of crime – based on finding black hair
- Signed statement retracted

Mechanisms of Normal Memory Function

- Encoding
- Storage/consolidation
- Retrieval
- Explicit (declarative) vs implicit (nondeclarative)
- Long term memory influenced by active inhibition as well as reinforcing of memory traces

Hippocampus



"Sea horse"

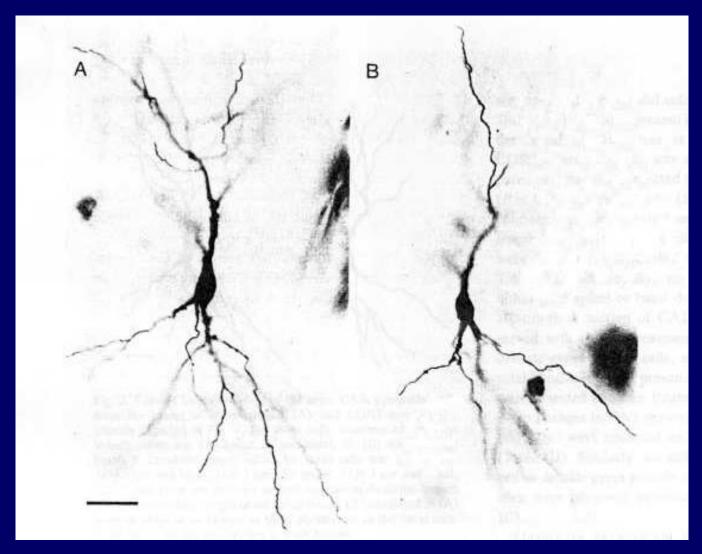
- Plays a critical role in learning and memory
- Creates a mental map of events in space and time
- Sensitive to stress
- Involved in dissociation and fear inhibition

Trauma & Memory in Forensic Settings

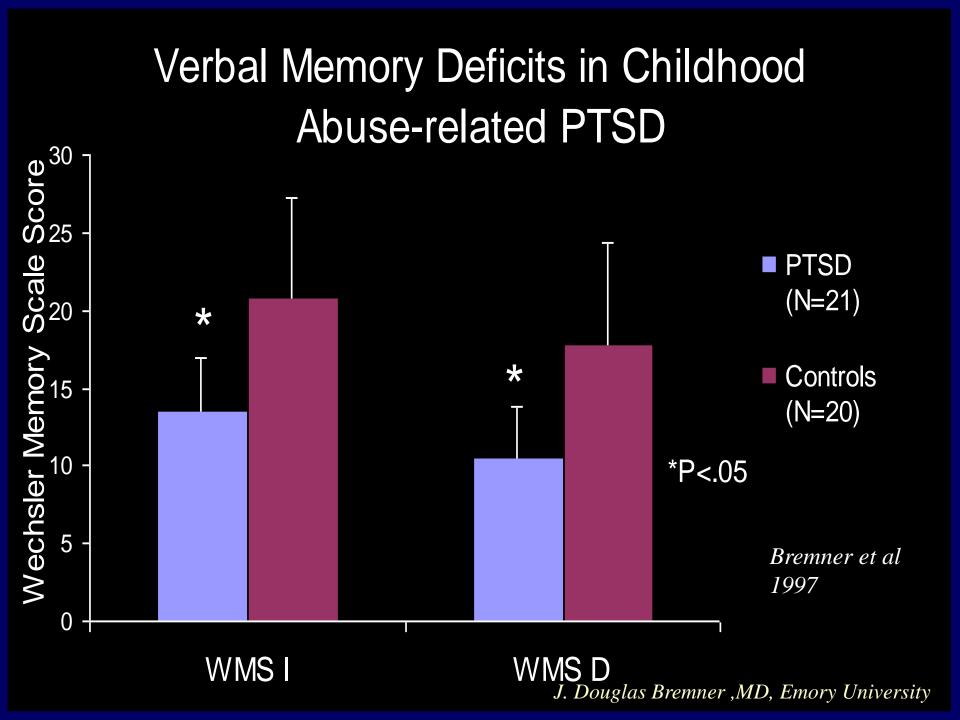
- Memory subject to deletions, distortions, insertions
- Studies of flashbulb memories Challenger explosion - source amnesia, repetition effects
- Story of spilling the punch bowl as a child at a wedding – confabulation with repeat interviews

Non-Stressed

Stressed

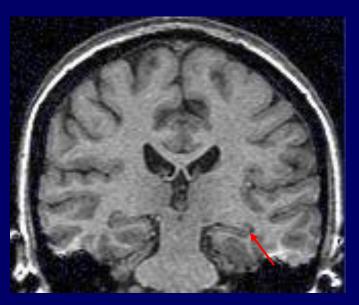


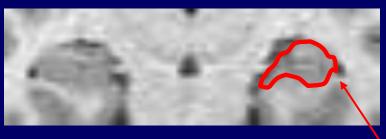
Stress results in decreased dendritic branching of neurons in the CA3 region of the hippocampus (Woolley et al. 1990)



Hippocampal Volume Reduction in PTSD









NORMAL

PTSD

Bremner et al., Am. J. Psychiatry 1995; 152:973-981.

Bremner et al., Biol. Psychiatry 1997; 41:23-32.

Gurvits et al., Biol Psychiatry 1996;40:192-199.

Stein et al., Psychol Med 1997;27:951-959. DeBellis 1999-no change in children with PTSD

J Douglas Bremner, MD, Emory University

Trauma & Memory in Forensic Settings

- Desert Storm veterans showed significant inconsistency in recall of traumatic events after return, and 2 and 6 year follow-up
- Veterans convinced of correctness of recall
- Inconsistency correlated with severity of PTSD symptoms
- Similar findings in rape survivors (Foa et al)

Trauma & Memory in Forensic Settings

- Bosnian war crimes tribunal in The Hague
- Key witness in prosecution of war crimes inconsistent recall of traumatic rape event
- Defense argument for effects of stress on memory, both acutely and with chronic PTSD
- Prosecution argued hyper-mnemesia with traumatic events (soldier not there)

thread pin eye sewing sharp point prick thimble haystack thorn hurt injection syringe cloth knitting

sharp wallet prick needle thimble knitting

thread pin eye sewing sharp point prick thimble haystack thorn hurt injection syringe cloth knitting

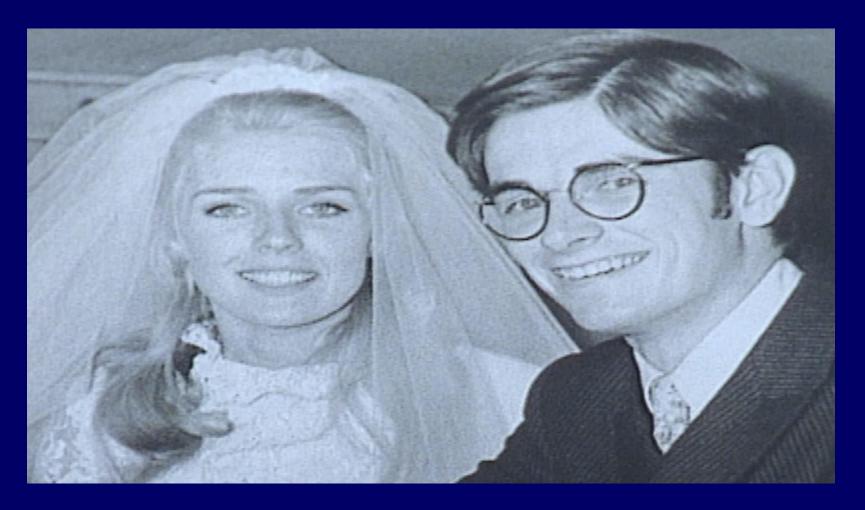
Increased False Memory with Deese Paradigm in PTSD

Table 3. Proportion of recognized nonstudied critical lures, previously studied words, and nonstudied words other than critical lures

Kind of word	Abused, PTSD women $(n = 23)$	Abused, non-PTSD women $(n = 13)$	Nonabused, non-PTSD women (n = 16)	Nonabused, non-PTSD men (n = 11)	F	p
Nonstudied critical lure	.95 ± .22	.78 ± .42	.79 ± .40	.86 ± .35	5.79*	.0007
Previously studied word Nonstudied word other than	.93 ± .26	$.90 \pm .31$	$.99 \pm .10$	$.93 \pm .27$	n.s.	n.s.
critical lure	$.26 \pm .44$	$.13 \pm .34$	$.23 \pm .42$	$.12\pm .44$	2.94**	.03

Note. PTSD = posttraumatic stress disorder.

^{*}Abused, PTSD group greater than other groups by Duncan's multiple-range test, p < .05. **Abused, PTSD group greater than abused, non-PTSD group and men by Duncan's multiple-range test, p < .05.



Betty and Dan Broderick on their Wedding Day in 1969

- Sold Tupperware door to door with a child on her hip
- Put husband through medical and law school at Notre Dame, Harvard and Princeton
- First child slept in a dorm room bureau drawer
- Dan promised to love Betty 'till death do them part.'

- Dan left Betty for a younger, identical version of herself
- Betty couldn't find a lawyer to go against Dan
- Betty said going against Dan in court was like putting a housewife in the ring with Muhammed Ali
- Dan filed for divorce in 1985: He got custody of the kids, the house, and all the money

- Betty ferried her kids to various activities in her SUV
- Her SUV had a license plate that read 'loademup'
- One day she drove that SUV right into the house where Dan was in bed with his new girlfriend

- Betty got a key to the house from her kids
- One night let herself into the house and shot and killed Dan and his new girlfriend in bed
- Betty went to prison
- She is in the same prison as Charles Manson but gets less reviews for parole hearings
- Betty Broderick: "Everyone wants kittens but no one wants a cat."

OJ Simpson: Sprinting Toward a Verdict of Not Guilty



OJ Simpson sprinting through the airport in a Hertz Rent-a-car commercial

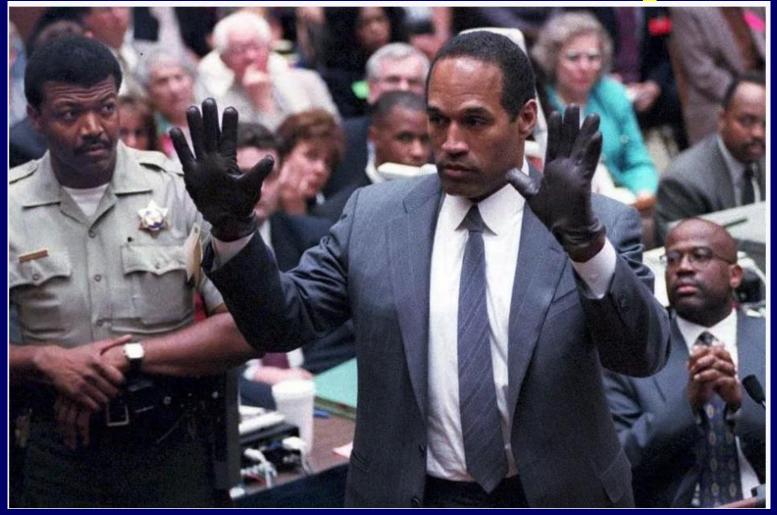
OJ Simpson: Sprinting Toward a Not Guilty Verdict

- OJ Simpson led police on a low speed chase in his white SUV
- Named as a suspect in the killing of his ex wife Nicole Brown Simpson and her boyfriend
- Lined up a dream team of lawyers
- Case revolved around bloody glove found in his home

OJ Simpson: Sprinting Toward a Not Guilty Verdict

- OJ Simpson trial nationally televised
- Exposed racial divisions regarding attitudes toward justice
- Tapes made by screenwriter of detective Mark Fuhrman using racial slurs led to demise of prosecution's case
- Case highlighted role of social media and significance of attitudes about race

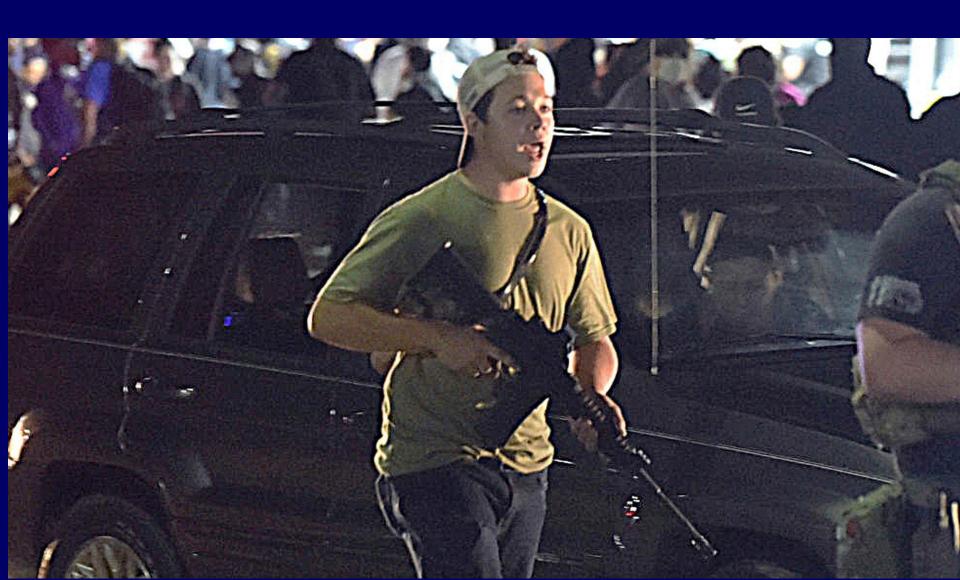
OJ Simpson: Sprinting Toward a Verdict of Not Guilty



"If the glove doesn't fit, you must

OJ Simpson: Sprinting Toward a Not Guilty Verdict

- Defense lawyers outlined scenario that OJ was a victim of racism in national magazine
- Planted idea that Fuhrman had planted the glove in OJ's home
- This raised doubt about DNA evidence
- Prosecutor asked OJ to put on glove



- August 25, 2020, protests broke out in Kenosha, Wisconsin, over police killing of a black man named Jacob Blake
- National Guard brought in after property destruction occurred
- Kyle Rittenhouse answered call on FB to join armed right wing militia to protect a car dealership damaged the night before

- Joseph Rosenbaum was released that day from a psychiatric admission for mania, noted to be acting erratic
- He chased Rittenhouse who claims he heard someone say "get him and kill him."
- Someone else fired a shot in the air

- Rosenbaum lunged at Rittenhouse and threw a bag with clothes and deodorant at him and tried to take his rife
- Rittenhouse fired four shots at Rosenbaum, killing him
- A crowd chased Rittenhouse
- A scuffle ensued, Rittenhouse fell and was kicked, he fired several shots

Kyle Rittenhouse

- Anthony Huber swung a skateboard at Rittenhouse's head and grabbed for his rifle
- Rittenhouse shot and killed Huber
- Gaige Grosskreutz filmed the scene. He pointed a gun at Rittenhouse
- Rittenhouse shot Grosskreutz in the arm. He survived.

Kyle Rittenhouse

- Rittenhouse charged with multiple counts of murder, pleaded self defence
- Became hero of gun rights advocates and the right wing
- Represented by QAnon believer, Trump advocate and lawyer Lin Wood of Atlanta
- Later had falling out with Wood whom he called "crazy".

George Floyd. 'I Can't Breathe'



- May 25, 2020, 46-year-old black male named George Floyd bought a pack of cigarettes with a twenty dollar bill at Cup Foods in Minneapolis, Minnesota
- Clerk said it was counterfeit, asked for the cigarettes back. Floyd refused
- Clerk called 911, said Floyd "awfully drunk" and "acting erratically."

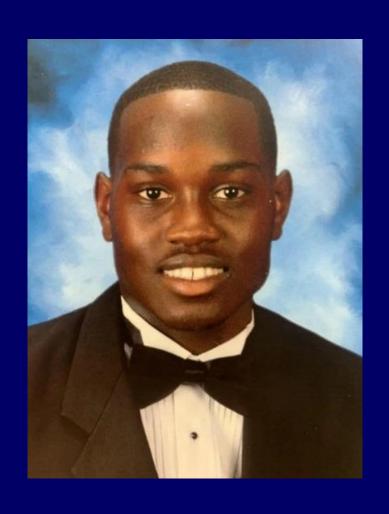
- Police officers tapped on window, asked Floyd to show his hands
- Floyd pulled from car and handcuffed
- Asked if he'd been using drugs, Floyd said he'd been "hooping"
- Floyd said he wasn't resisting arrest, but had claustrophobia about getting in the police car
- Floyd struggled and said 'I can't breathe'

- Officer Derek Chauvin arrives, puts Floyd on ground with knee on his neck
- Crowd gathers, videotaping, and tell officers to let him go while Floyd says 'I can't breathe'
- Floyd unresponsive after six minutes
- Chauvin kneels on him for 9 minutes 29 sec
- Floyd taken to hospital, pronounced dead.

- Autopsy showed Floyd had fentanyl and methamphetamine in his system
- 90% occlusion of a coronary artery
- Cause of death cardiopulmonary arrest "complicating law enforcement subdual, restraint and neck compression."

- Nation wide protests erupted after circulation of video
- Case shows power of social media to change events
- Chauvin convicted of murder

Ahmaud Arbery: 'There's a Black Male Running Down the Street'



Ahmaud Arbery 'There's a Black Male Running Down the Street'

- Call in to Glynn Co. GA 911 'There's a black male running down the street'
- Operator: 'What did he do wrong?'
- Response: 'He's running down the street.'
- Greg and Travis McMichael give chase in their truck after seeing him in construction site

Ahmaud Arbery: 'There's a Black Male Running Down the Street'



McMichaels cut off Arbery with their truck in Satilla Shores, Glynn County, Georgia

Ahmaud Arbery 'There's a Black Male Running Down the Street'

- Travis struggles with Arbery, shoots him
- William Bryan follows and videotapes events
- DA Jackie Johnson worked with Greg M. and doesn't press charges
- Media exposure leads Georgia Bureau of Investigation to investigate

Ahmaud Arbery: 'There's a Black Male Running Down the Street'



Gregory McMichael, Travis McMichael, William Bryan convicted of murder, McMichaels sentenced to life without parole

Two Trials, Two Outcomes

- Rittenhouse legally had right to carry gun
- Jury found he acted in self defense
- Prosecutors in Arbery case argued 'it's not self defense if you started it.'
- Arbery did not break any law, was in open construction site with no signage to not trespass, didn't steal anything



- Rebecca Zahau lived in Spreckels mansion with boyfriend
- Jonah Shacknai millionaire owner of pharmaceutical company
- 5-year-old Max fell off balcony in house

Rebecca Zahau

- Brother Adam Shacknai flies in to stay
- Rebecca found hanging from balcony after Max's accident
- Hands tied behind back, legs bound, t shirt in mouth
- No disturbance of dust on rail
- Rope tied to bed, doesn't move
- Door to bedroom closed



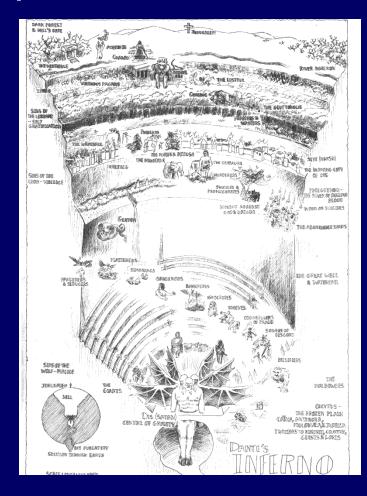


"She saved him, can you save her."

- Police determine it a suicide
- Case receives wide publicity
- Adam Shacknai later loses civil suit

Litigators 12 Circles of Hell

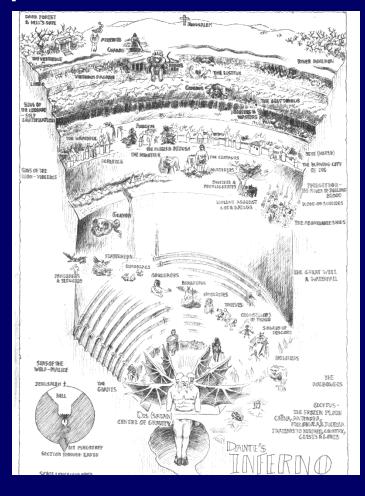
Adapted from Dante



Civil Rights Consumer Protection Family Trusts and Wills Toxic Torts **Intellectual Property** Corporate **Taxation** Criminal Malpractice Bankruptcy Personal Injury **Product Liability**

Litigators 12 Circles of Hell

Adapted from Dante



Civil Rights Consumer Protection Family Trusts and Wills Toxic Torts Intellectual Property Corporate **Taxation** Criminal Malpractice Bankruptcy Personal Injury **Product Liability**

Accutane (isotretinoin)

- Isotretinoin--mechanism of action
- Decreases sebum production
- Normalizes follicular hyperkeratinization and reduces follicular plugging
- Decreases Propionibacterium acnes colonization
- Anti-inflammatory

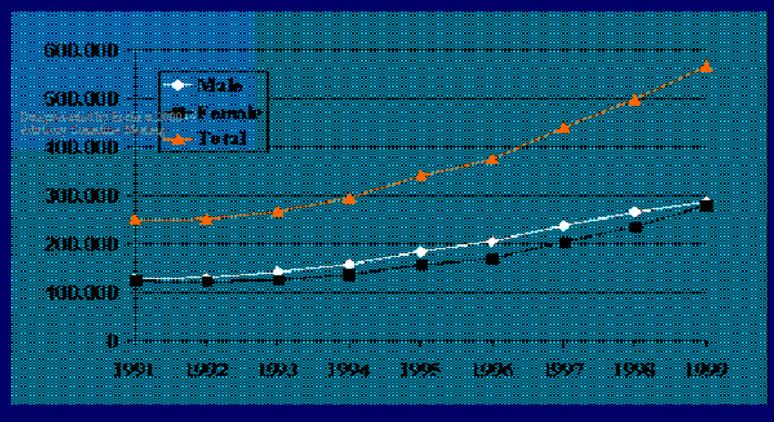
Accutane and Birth Defects

- Isotretinoin--Teratogen
- Increased risk of spontaneous abortion and premature birth
- Malformations: craniofacial, cardiac, thymus, CNS, functional 28% of exposed pregnancies affected at birth
- Indicated only for use in females who are not pregnant and males

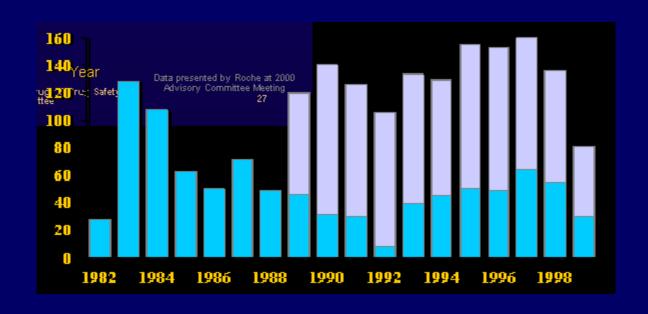
Accutane and Adverse Events

- Birth defects; decreased IQ (50%)
- Depression, suicide, violence, aggression, psychosis
- Irritable bowel syndrome
- Bone (and joint and muscle) problems
- Increased lipids
- Hearing and vision problems
- Pseudotumor cerebri

Continued Popularity of Presribing of Accutane in the 1990s



Pregnancies Occurring While on Accutane



Factors Involved in Causality

- Case reports
- Temporal association
- Challenge/dechallenge/rechallenge
- Dose Response
- Biological plausability
- Class Effect

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Author	Number	Depression	Suicidal	Psychosis	Violence & Aggressio n	Onset	De challenge	Re challenge
Hazen 83	6/110	+++++				2 wks		
Bruno 84	10/94	++++++++				During treatm ent		
Lindemayr 86	1	+	+C			2 mos		
Burket 87	1	+				20 wks	+	
Bigby 88	3	+++	+			6 wks, 2 mos	+	
Villalobos 89	1			+		2 wks	+	+
Scheinmann 90	7/700	+++++	+		Irritability	During treatm ent	+++++	+
Hepburn 90	1	+	+		+	2 mos	+	
Gatti 91	1	+	+ C			1 mo after Rx		
Bravard 93	3	+++	+, +C			2 mos, 3 mos (2)		
Duke 93	2	++	+	+	+	1 mo (2)	++	
Byrne 95	3	+++				During Rx 2		

Table 1 (con). Case Reports of Behavioral Effects of Isotretinoin										
Author	Number	Depression	Suicidal	Psychosis	Violence & Aggression	Onset	De challenge	Re challenge		
Aubin 95	1		+			1 day				
Cotterill 97	2		+C, +C			2 mos				
Cott 99	1	+		+		4 wks	+			
Middelkoop 99	1	+	+ C			During treatment				
Hull 00	5/121	+++++				During treatment				
Pitts 00	41	41				During Rx	41	41		
Ng 01	1	+	+		+	2 wks	+	+		
Wysowski 01	431	394	37 C							
Ng 02	5/174	+++++				During treatment	+			
Robusto 02	1	+				During treatment				
Van Broekhaven 03	1	+	+ C			During treatment				
La Placa 05	1	+			+	5 wks				

Friedman et al 2005

- Subjects were 18-21 years old members of the Israel Defense Forces.
- 1,419 with acne treated with isotretinoin and 1102 with psoriasis who were not treated with isotretinoin.
- Mental health services utilization over a 5 year period in isotretinoin versus psoriasis patients was 17.2% v 12.5% (p=.0003).
- There was also an increase in suicidal ideation/suicide attempt (7.5% v 3.5%, p=0.04).
- Authors concluded findings were consistent with psychiatric side effects of isotretinoin.

- Hull and Demkiw-Bartel (2000) studied 121 patients treated with isotretinoin and found evidence of depression in 5 (4%) that persisted throughout the course of treatment. Other symptoms included fatigue (26%), headache (7%), and weight loss (3%).
- Hazen et al (1983) reported that 6/110 (5.5%) patients with acne or related disorders treated with 1-2 mg/kg/day isotretinoin developed symptoms of depression, including depressed mood, crying spells, malaise, or forgetfulness, within two weeks of initiation of the medication.

- Scheinman et al (1990) reported on seven cases of depression associated with Accutane administration from a larger clinical trial in 700 patients.
- In 5/7 patients, symptoms of depression developed during the first course of treatment of Accutane.
- Symptoms of depression included depressed mood, fatigue, irritability, sadness, decreased concentration, crying spells, loss of motivation, forgetfulness, and loss of pleasure. One patient had suicidal ideation.
- Three of the patients had headaches, which received with discontinuous

- Bruno et al. (1984) reported on 94 patients treated with variable doses of isotretinoin and ten subjects with acne not in treatment.
- 11% of patients reported depression. In patients treated with high doses, 7% reported insomnia, 22% fatigue, 11% headache, 7% weight loss, 2% impotence, and 9% loss of libido, while no subjects with untreated acne reported these side effects.

- Thus rates of depression from 1% (Scheinman) to 3% (Ng) to 4% (Hull) to 5.5% (Hazen) to 11% (Bruno) (overall average 3-4%)
- These rates are higher than what would be expected in the general population over the course of a 4 month treatment trial for the incidence of new onset depression, which should be about .5% (Eaton et al., 1989).
- 800 subjects to show an effect in a clinical trial

Wysowski et al 2001 FDA Reports

- Reports of depression and suicide to the Food and Drug Administration (FDA) in patients treated with isotretinoin from 1982 to May 2000 that were entered in the Adverse Event Reporting System database.
- 37 reports of patients treated with isotretinoin who committed suicide
- 110 who were hospitalized for depression, suicidal ideation or suicide attempt
- 284 with no hospitalized depression
- Total of 431 patients.
- The cases also showed evidence of a temporal relationship between administration of isotretinoin and the development of depression and positive de-challenges and re-challenges.
- Isotretinoin ranked in the top 10 of all drugs in the FDA database for reports of depression.

Challenge dechallenge rechallenge

- Removal of drug from patient causes symptom to go away, rechallenge causes return
- Considered sufficient in and of itself in the absence of any other factors to establish causality (Strom, 2005).
- Dr Marilyn Pitts presented 41 cases of positive dechallenge/ rechallenge reported to the FDA. She concluded the cases "provide strong evidence to support a link..." She also noted that depression was the 6th most common reported side effect of Accutane, much higher than rates reported for the comparable treatment of antibiotic. (presented at the September 18-19, 2000 FDA Advisory Committee meeting).

Challenge dechallenge rechallenge

- Scheinman et al (1990) reported 7 cases of depression associated with isotretinoin administration.
- Symptoms resolved in all cases after discontinuation of medication within 2-7 days. One of the patients was rechallenged with isotretinoin and experienced a recurrence of symptoms after 3 months.
- Ng et al (2001) reported a case who developed symptoms of depression two weeks after starting isotretinoin therapy.
- The symptoms improved with reduction of isotretinoin dose and treatment with sertraline.
- When the dose of isotretinoin was increased again the depressive symptoms returned, in spite of a clearing of acne, with an associated suicide attempt.
- When the dose was stopped the symptoms resolved.

Challenge dechallenge rechallenge

- Wysowski et al (2001) described a case who during a 3-4 month course of isotretinoin therapy developed personality changes, mood swings, and depression.
- After completion of treatment he returned to normal.
- The patient developed the same symptoms, with another isotretinoin treatment but returned to normal at the end of treatment.
- Sometime later he started a third course of treatment. This time his symptoms recurred and persisted after the end of isotretinoin treatment.

Dose Response

- If side effects increase with an increased dosage, this indicates a pharmacological result tied to dosage.
- Meyskens (1982) reported that 25% of his patients receiving doses of 3 mg/kg/day of isotretion (3-6 time higher than the dose used for acne) developed symptoms of depression (i.e. much higher than the 3-4% reported in most other series). The author concluded that "psychologic changes may be dose related."
- Pitts (2000) reported six cases where symptoms of depression resolved when the dose was reduced, concluding "possible dose response"

Dose Response

- Ng et al (2001) reported a case of depression improved with reduction of isotretinoin dose and treatment with sertraline. When the dose of isotretinoin was increased depressive symptoms returned, with associated suicide attempt.
- Bruno compared acne patients taking high dose isotretinoin (.75-1.21 mg.kg/day) to low dose (0.75-1.21 mg/kg/day). Symptoms related to depression were higher in high dose versus low dose, including depressed libido (9% of high dose versus 2% of low dose), impotence (2% versus 0%), and weight loss (7% versus 0%). These symptoms were higher than a group of acne patients not on isotretinoin, who reported none of these symptoms.

Mechanism of Action

- Biologically plausible mechanism for a drug to exert an effect
- Pseudotumor cerebri.
- Retinoids effect on the brain; turning genes on and off.
- Isotretinoin inhibits hippocampal nerve growth in mice.
- Causes depression behaviors in mice
- Decreases orbitofrontal function in acne patients

Chemical Structures of Isotretinoin (Accutane) and Vitamin A

H₃C CH₃ CH₃ OH

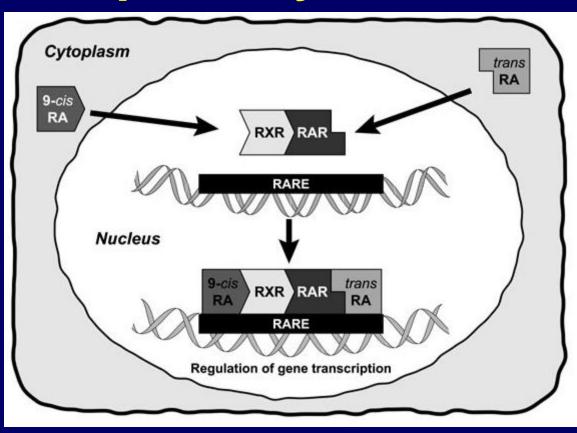
Vitamin A (Retinol)

/ [Retinaldehyde Dehydrogenase 2] Retinoic Acid (13-trans retinoic acid)

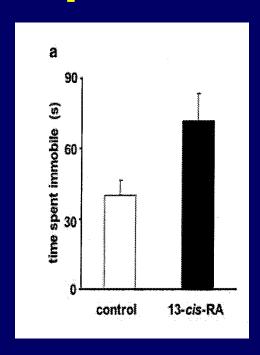
Retinal

Isotretinoin (13-cis-retinoic acid)

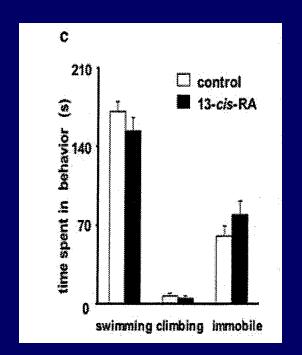
Regulation of Gene Transcription by Retinoic Acid



Isotretinoin Associated with Depression Behaviors in Mice

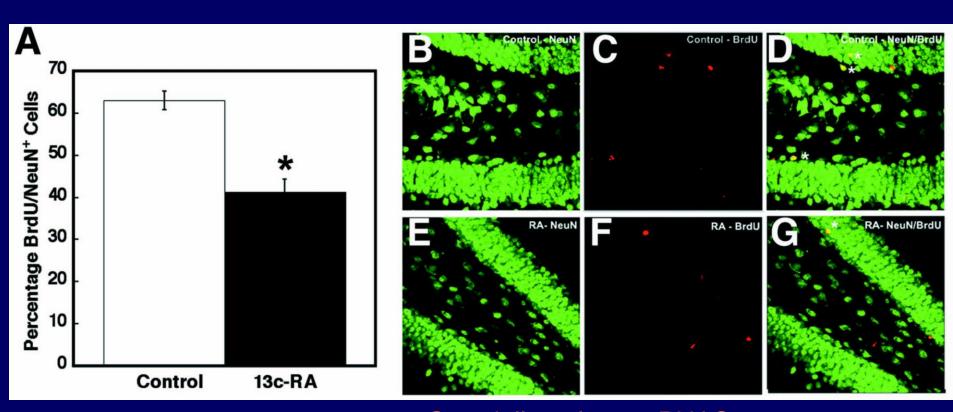


Increased time immobile in tail suspension test



Increased time immobile in forced swim test

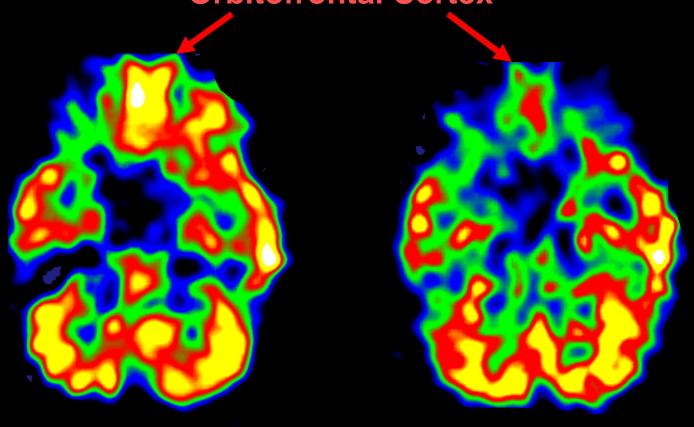
Decreased Hippocampal Neurogenesis with Isotretinoin



Crandall et al 2005 PNAS

Decreased Metabolism in Orbitofrontal Cortex with AMPT Induced Return of Depressive Symptoms

Orbitofrontal Cortex



Normal

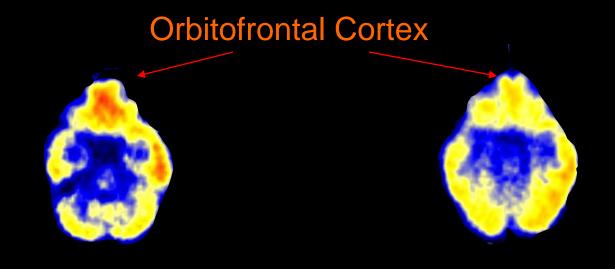
Depressed

Bremner et al JAMA 2003

Brain Metabolic Correlates of Isotretinoin Administration in Acne Patients

- Patients treated for 3 months with Accutane (N=13) or antibiotic (N=15)
- All patients underwent brain imaging with positron emission tomography (PET) measurement of brain metabolism before and after treatment
- Decreased orbitofrontal metabolism with Accutane (-21%) but not antibiotic (+1%)
- No effect on depression measured with Ham

Effects of Isotretinoin (Accutane) on Brain Function in Acne Patients



Pre-accutane

Post-accutane

Isotretinoin Associated with Decreased Function in Orbitofrontal Cortex

Bremner et al American Journal of Psychiatry 2005

Class Effect

- Medications in same class cause similar side effects
- Vitamin A: Active form is isomer of isotretinoin (same molecular, different shape)
- Vitamin A causes pseudotumor cerebri
- Ingestion associated with psychosis, depression and mental disorders

Vitamin A Toxicity

- 32 y/o female treated with Vitamin A for acne, developed lethargy, decreased interest in things, bone pain, resolved with discontinuation (WH Stimson, NEJM, 1961; 263(8)369-371)
- Described 6 other cases with toxicity including headache
- Headache, diploplia, increased CSF pressure with Vitamin A toxicity more common in children
- Ingestion of polar bear liver with high Vitamin A concentration in artic explorers led to psychosis, confusion

Behavioral Effects of Polar Bear Liver

Livers of polar bears and other arctic Animals high in Vitamin A; explorers Who ate them developed psychosis, agitation Depression, and other behavioral effects; Also dechallenge-rechallenge

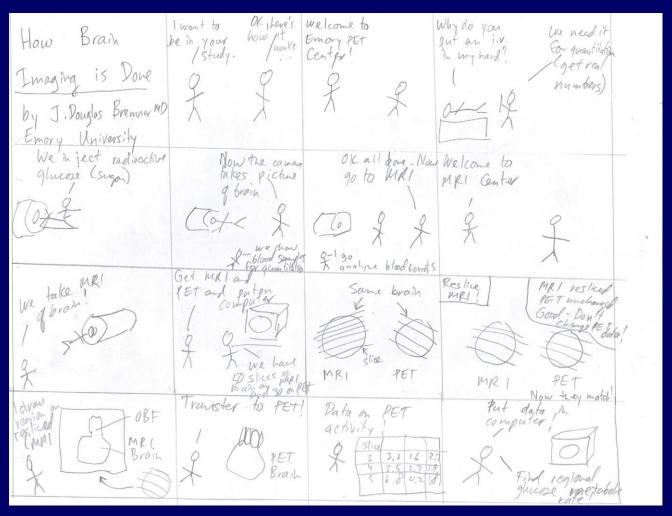




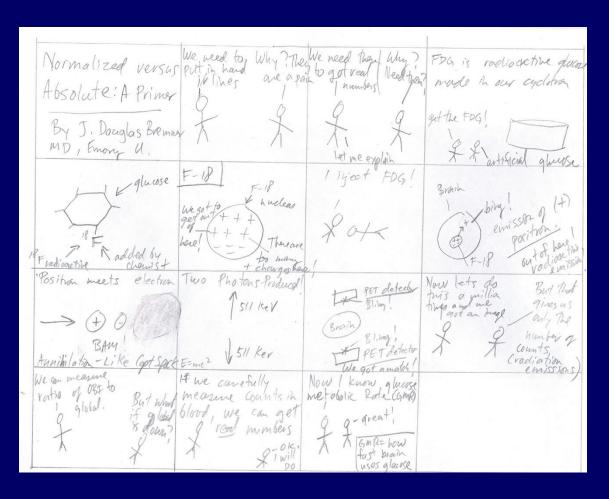




How to be an Expert Witness: Let's Learn about Brain



How to be an Expert Witness: Teaching the Lawyers



How to be an Expert Witness

- Only answer the questions asked (don't elaborate, it usually leads to somewhere you don't want to go)
- Don't joke or be sarcastic (you are not there to become friends with the opposing counsel)
- Don't be an advocate; you are a neutral authority, not an employee of counsel
- Take your time answering questions

How to be an Expert Witness

- If you don't understand the question, say so.
 If the question makes no sense, say so.
- You don't have to answer categorical yes/no questions. The answer often depends on the situation and an evaluation of all of the information available.
- Ditto for the ultimate authority. All of the information must be considered

Physiology and False Memories: Role of Mental Health in Justice System

- Mental health professionals can add in expertise on psychiatric disorders, memory, eyewitness testimony, coerced confessions
- Media and social media playing an increasingly outsize role in judicial process, affecting social processes
- Mental health professionals have power over individuals that can be misused
- Drug safety a specific area of expertise