Advances in Drug Abuse and Addiction Research from NIDA: Implications for Treatment

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Addiction Medicine: Improving Clinical and Teaching Skills for Generalists
2011 Chief Resident Immersion Training (CRIT) Program
Cape Cod, Massachusetts
May 2011
Bringing the Full Power of Science to Bear on Drug Abuse & Addiction
## Estimated Economic Cost to Society Due to Substance Abuse and Addiction:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>$193 billion/year</td>
</tr>
<tr>
<td>Alcohol</td>
<td>$235 billion/year</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>$181 billion/year</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$609 billion/year</strong></td>
</tr>
</tbody>
</table>

Source: ONDCP, 2004; CDC, 2007; Rehm et al., 2009 Lancet 373:2223-33
What is Addiction?
Addiction is A Brain Disease

- Characterized by:
  - Compulsive Behavior
  - Continued abuse of drugs despite negative consequences
  - Persistent changes in the brain’s structure and function
Advances in science have revolutionized our fundamental views of drug abuse and addiction.
Your Brain on Drugs in the 1980's

this is your brain on drugs.
Your Brain on Drugs – Now

Source: Lee et al., 2009 J Neurosci 29:14734-40.
NIDA Research

From Molecules...

...To Managed Care

...Drug Courts

...Community Coalitions
What have we learned?
Addiction is Like Other Diseases…

- It is preventable
- It is treatable
- It changes biology
- If untreated, it can last a lifetime

Decreased Heart Metabolism in Heart Disease Patient

Decreased Brain Metabolism in Drug Abuser

Healthy Heart

Diseased Heart

Healthy Brain

Diseased Brain/Cocaine Abuser
In 2009, an estimated 21.8 million Americans, or 8.7 percent of the population aged 12 or older, were current illicit drug users.

Source: National Survey on Drug Use and Health (NSDUH), SAMHSA, 2010
Percent of Students Reporting Any Illicit Drug Use in Past Year, by Grade

SOURCE: University of Michigan, 2009 Monitoring the Future Study
Percentage of U.S. 12th Grade Students Reporting Past Month Use of Cigarettes and Marijuana, 1975 to 2010

SOURCE: University of Michigan, 2010 Monitoring the Future Study

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After Marijuana, Prescription and Over-the-Counter Medications* Account for Most of the Commonly Abused Drugs

Prevalence of Past Year Drug Use Among 12th Graders

- Marijuana/Hashish
- Vicodin*
- Amphetamines*
- Cough Medicine*
- Adderall*
- Tranquilizers*
- Salvia
- Hallucinogens
- OxyContin*
- Sedatives*
- MDMA (Ecstasy)
- Inhalants
- Cocaine (any form)
- Ritalin*

*Categories not mutually exclusive
Why Do People Take Drugs in The First Place?

To Feel Good
To have novel: feelings sensations experiences
AND to share them

To Feel Better
To lessen: anxiety worries fears depression hopelessness
Initially, A Person Takes A Drug Hoping to Change their Mood, Perception, or Emotional State

Translation---

...Hoping to Change their Brain
Drugs can be “Imposters” of Brain Messages

Brain's Chemical

Anandamide

Drug

THC
Addiction

Reward & well-being

Motivation

Dopamine

Movement
The Neuron: How the Brain’s Messaging System Works

Cell body (the cell's life support center)

Dendrites

Axon

Myelin sheath

Neuronal Impulse

Terminal branches of axon
dopamine

dopamine receptor
dopamine transporters
Natural Rewards Elevate Dopamine Levels

Effects of Drugs on Dopamine Release

**Amphetamine**

- Graph showing the effect of Amphetamine on Dopamine (DA), DOPAC, and HVA levels in the Accumbens area over time.

**Cocaine**

- Graph showing the effect of Cocaine on Dopamine (DA) and DOPAC levels in the Accumbens area over time.

**Nicotine**

- Graph showing the effect of Nicotine on Dopamine and DOPAC levels in the Accumbens and Caudate areas over time.

**Morphine**

- Graph showing the effect of Morphine on Dopamine (DA) and DOPAC levels in the Accumbens area over time.

Di Chiara and Imperato, PNAS, 1988

Di Chiara and Imperato, PNAS, 1988
Vulnerability

Why do some people become addicted to drugs while others do not?
Addiction Involves Multiple Factors

Biology/Genes  <->  Environment

DRUG

Brain Mechanisms

Addiction
Genetics is a Big Contributor to the Risk of Addiction…

And…

The Nature of this Contribution Is Extremely Complex
Gene Cluster is Associated with Nicotine Dependence

**IMMEDIATE COMMUNICATION**

α-5/α-3 nicotinic receptor subunit alleles increase risk for heavy smoking

W Berrettini1,2,4, X Yuan5,2, F Tozzi3, K Song2,2, C Francks2,2, H Chilcoat4, D Waterworth2,3, P Muglia2,3,6 and V Mooser2,3

**ARTICLE IN PRESS**

The CHRNA5/A3/B4 Gene Cluster Variability as an Important Determinant of Early Alcohol and Tobacco Initiation in Young Adults

Isabel R. Schlaepfer, Nicole R. Hoft, Allan C. Collins, Robin P. Corley, John K. Hewitt, Christian J. Hopfer, Jeffrey M. Lessem, Matthew B. McQueen, Soo Hyun Rhee, and Marisla A. Brininger

A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

Thorgeir E. Thorgeirsson1,6, Frank Geller1,6, Patrick Sulem1,6, Thorunn Rafnar1,6, Anna Wiste1,2, Kristinn P. Magnusson1, Andrei Manolescu1, Gudmar Thorleifsson1, Hreinn Stefansson1, Andres Ingason1, Simon N. Stenson2, Jon T. Rasmussen1, Jonnny Thorgeirsson1, Rolf D. Melchior1,10, Sveinn Thorgeirsson1,10, Kristján Magnusson1,10, Skuli Thorgeirsson1,10, Mani Saeed1,10, Thorgeir Thorleifsson1,10

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Some Gene Variants Implicated in Addiction

- **FAAH** - associated with drug dependence
- **OPRM1** - associated with opiates and alcoholism
- **CYP2A6, CYP2B6** - associated with smoking and smoking cessation
- **ALDH2** - associated with protection against alcoholism
- **DBH** (Dopamine beta-hydroxylase) – cocaine-induced paranoia
- **DRD2, DRD4** (Dopamine receptors) - reward, craving
- **NrCAM, neurexins** (Cell adhesions genes) - assoc with drug abuse and addiction
- **Prodynorphin gene** - associated with protection against cocaine dependence
- **Nicotinic alpha 7 promoter** – assoc. with decreased expression of its message in different brains regions and with sensory gating defects in schizophrenics

-- **Alpha 5 and beta 3** (nicotinic receptors) – assoc. with nicotine dependence
-- **5HT1B** (serotonin receptor) - associated with conduct disorder and alcoholism
Individual Differences in Response to Drugs: DA Receptors influence drug liking

High DA receptor

Low DA receptor

As a group, subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant

Adapted from Volkow et al., Am. J. Psychiatry, 1999.
But it isn’t all genetics
Drug Abuse Risk Factors

Community

Peer Cluster

Family

Individual
What Environmental Factors Contribute to Addiction?

- Drug availability
- Peers who use drugs
- Early physical or sexual abuse
- Stress
Social Stressor Affects Brain DA D2 Receptors and Drug Self-Administration

Individually Housed

Becomes Dominant
No longer stressed

Group Housed

Becomes Subordinate
Stress remains

Reinforcers (per session)

Cocaine (mg/kg/injection)

What have we learned about other aspects of vulnerability?
Addiction Is a Developmental Disease
starts in childhood and adolescence

Age at tobacco, at alcohol and at cannabis dependence, as per DSM IV

National Epidemiologic Survey on Alcohol and Related Conditions, 2003

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Adolescents’ Brains Are Still Developing...

Implications for prevention and Treatment?

Maturation starts at the back of the brain ... and moves to the front

- **Judgment**
  - Prefrontal Cortex
- **Emotion**
  - Amygdala
  - Nucleus Accumbens
- **Motivation**
  - Cerebellum

**Physical coordination, sensory processing**

**Notice:** Judgment is last to develop!

Source: K. Winters
Do Adolescents React Differently than Adults to Substances of Abuse?
**Rats Exposed to Nicotine in Adolescence Self-Administer More Nicotine Than Rats First Exposed as Adults**

![Graph showing nicotine infusions and amounts infused per session for adolescent and adult exposure.](image-url)

Do We Need Fundamentally Different Strategies For Adolescents?
What Else Have We Learned?
Addictive Disorders Often Co-Exist With Mental Disorders

Mental Disorder

Addictive Disorder

Comorbid Disorders
Addictive Disorders Often Co-Exist With Mental Disorders

Serious Psychological Distress
24.3 million

Comorbid Disorders

Substance Use Disorder
5.4 million
15 million

Co-Occurrence of Serious Psychological Distress and Substance Use Disorder in the Past Year among Adults Aged 18 or Older: 2007

SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2007
What Other Biological Factors Contribute to Addiction—Comorbidity

Prevalence of Drug Disorders

- Any Mood Disorder
- Any Anxiety Disorder
- Depression
- Mania
- Panic w/ Agoraphobia
- Panic w/o Agoraphobia
- Social Phobia
- Generalized Anxiety

Prevalence of Nicotine Addiction

- General public
- Schizophrenia
- Depression
Many Common Factors Are Involved in Addiction and Mental Illness

Addiction:

• Early Physical or Sexual Abuse
• Stress
• Family History
• Mental Illness
• Peers who use Drugs

Mental Illness:

• Early Physical or Sexual Abuse
• Stress
• Family History
• Drug and Alcohol Abuse
Why do Mental Illnesses and Substance Abuse Co-occur?

• Self-medication
  – substance abuse begins as a means to alleviate symptoms of mental illness

• Causal effects
  – Substance abuse may increase vulnerability to mental illness

• Common or correlated causes
  – the risk factors that give rise to mental illness and substance abuse may be related or overlap
These may contribute to vulnerability to initial drug use.

But what happens to the brain over time?
Science Has Generated Much Evidence Showing That...

Prolonged Drug Use Changes the Brain In Fundamental and Long-Lasting Ways
AND...

We Have Evidence That These Changes Can Be Both Structural and Functional
Chronic cocaine increases density of dendritic spines and neuronal branching in the nucleus accumbens.

Functionally...

Dopamine D2 Receptors are Decreased by Addiction

Cocaine

Meth

Alcohol

Heroin

Control

Addicted

DA D2 Receptor Availability
Dopamine Transporters in Methamphetamine Abusers

Motor Task
Loss of dopamine transporters in methamphetamine abusers may result in slowing of motor reactions.

Memory Task
Loss of dopamine transporters in methamphetamine abusers may result in memory impairment.

But Dopamine is only Part of the Story

• Scientific research has shown that other neurotransmitter systems are also affected:
  – Serotonin
    • Regulates mood, sleep, etc.
  – Glutamate
    • Regulates learning and memory, etc.
Circuits Involved In Drug Abuse and Addiction
Memories Appear to Be A Critical Part of Addiction
Cocaine Abusers Have Increased Activation in Brain Regions Associated with Emotional Learning

Source: Childress, et al., AJP, 1999
But It’s Not Just Memories...
Drugs Usurp Brain Circuits and Motivational Priorities
We Don’t Know the Exact Switch
BUT...
We Do Know that the Brain Circuitry Involved in Addiction Has Similarities to that of Other Motivational Systems
Cocaine Craving:
Population (Cocaine Users, Controls) x Film (cocaine)

Garavan et al. A. J. Psych 200

Signal Intensity (AU)

Controls   Cocaine Users

Cingulate
Ant Cing
IFG

Garavan et al A .J. Psych 200
Cocaine Craving:
Population (Cocaine Users, Controls) x Film (cocaine, erotic)

Garavan et al A. J. Psych 200

Controls      Cocaine Users

Cingulate
Ant Cing
IFG

Garavan et al A. J. Psych 200
This Results in “Motivational Toxicity” and Compulsive Drug Use (Addiction)
Addiction is Fundamentally a Brain Disease
The Brains of Addicts Are Different From the Brains of Non-Addicts

...And Those Differences Are An Essential Element of Addiction
But Addiction is Not Just a Brain Disease
Addiction is a Brain Disease
Expressed as Compulsive Behavior

It is the Quintessential Biobehavioral Disorder
So.....

.....What Does This Mean For Treatment?
Circuits Involved In Drug Abuse and Addiction

All of these brain regions must be considered in developing strategies to effectively treat addiction.
Why Can’t Addicts Just Quit?

Because Addiction Changes Brain Circuits

Non-Addicted Brain

Addicted Brain

Adapted from Volkow et al., Neuropharmacology, 2004.
Decrease the rewarding value of drugs
Vivitrol significantly increases percentage of patients with opioid-free weeks.
Antibodies can reduce brain concentrations

Capillary Blood Flow

Antibody holds drug in bloodstream

Brain
Fewer cocaine urines at higher vaccine dose

Kosten, et al, 2010 Arch Gen Psych
Decrease the rewarding value of drugs

Increase the rewarding value of non-drug reinforcers
Contingency Management for the Treatment of Methamphetamine Use Disorders

![Bar chart showing mean number of samples negative for stimulants and alcohol and mean weeks of abstinence for contingency management (N=51) versus treatment as usual (N=62).]

![Line graph showing percent of samples negative for stimulants and alcohol over weeks for contingency management (N=51) versus treatment as usual (N=62).]

Weaken learned positive associations with drugs and drug cues

Increase the rewarding value of non-drug reinforcers

Decrease the rewarding value of drugs

Strengthen frontal control
Behavioral Interventions
Medications
Biofeedback
Treating A Biobehavioral Disorder Must Go Beyond Just Fixing The Chemistry
The Most Effective Intervention Strategies Will Attend to All Aspects of Addiction:

- Biology
- Behavior
- Social Context
Drug Abuse Treatment Core Components and Comprehensive Services

- Medical
- Mental Health
- Legal
- Educational
- Vocational
- Financial
- Housing & Transportation
- Child Care
- Family
- AIDS / HIV Risks
- Core Treatment
  - Intake Assessment
  - Treatment Plans
  - Group/Individual Counseling
  - Abstinence Based
  - Pharmacotherapy
  - Self-Help (AA/NA)
  - Urine Monitoring
  - Case Management
  - Continuing Care

Etheridge, Hubbard, Anderson, Craddock, & Flynn, 1997 (PAB)
In Treating Addiction...

We Need to Keep Our Eye on the Real Target

Abstinence

Functionality in Family, Work and Community
Extended Abstinence is Predictive of Sustained Recovery

After 5 years – if you are sober, you probably will stay that way.

It takes a year of abstinence before less than half relapse.

<table>
<thead>
<tr>
<th>Duration of Abstinence at Year 7</th>
<th>% Sustaining Abstinence through Year 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 12 months (n=157; OR=1.0)</td>
<td>36%</td>
</tr>
<tr>
<td>1 to 3 years (n=138; OR=3.4)</td>
<td>66%</td>
</tr>
<tr>
<td>3 to 5 years (n=59; OR=11.2)</td>
<td>86%</td>
</tr>
<tr>
<td>5+ years (n=96; OR=11.2)</td>
<td>86%</td>
</tr>
</tbody>
</table>
But, drug addiction is a chronic disease with relapse rates similar to those of other chronic illnesses.

We Need to View and Treat Addiction As A Chronic, Relapsing Illness
Outcome In Hypertension

Pre - During - Post
Outcome In Addiction

Pre - Post

Pre

During

Post

Treatment Research Institute
If we treat a diabetic and symptoms don’t subside….what do we do?

Would we increase the dose?
Would we change medications?
Would we change treatment approaches?

Would we fail to provide ongoing treatment for a diabetic?
Addiction is Similar to Other Chronic Illnesses Because:

- It has biological and behavioral components, both of which must be addressed during treatment.

- Recovery from it—protracted abstinence and restored functioning—is often a long-term process requiring repeated episodes of treatment.

- Relapses can occur during or after treatment, and signal a need for treatment adjustment or reinstatement.

- Participation in support programs during and following treatment can be helpful in sustaining long-term recovery.

Therefore…
Full recovery is a challenge but it is possible ...
BRAIN RECOVERY WITH PROLONGED ABSTINENCE

Healthy Person

METH Abuser
1 month abstinence

METH Abuser
1-4 months abstinence
Treatment Reduces Drug Use and Recidivism

Delaware Work Release Therapeutic Community (CREST) + Aftercare 3 Years After Release (N=448)

- **Drug-Free**: 5, 17*, 27*, 35*  
  - No treatment  
  - CREST Dropouts  
  - CREST Completers
  - CREST Completers + Aftercare

- **Arrest-Free**: 29, 28, 55*, 69*  
  - No treatment  
  - CREST Dropouts  
  - CREST Completers
  - CREST Completers + Aftercare

*p < 0.05, compared to no treatment group*
Research  

NIDA Physician Outreach  

Practice
How is substance abuse relevant to primary care?

Substance abuse can:

- Lead to **unintentional injuries**
- **Exacerbate medical conditions**
- **Exacerbate psychiatric problems** (anxiety, depression)
- **Induce medical diseases** (stroke, cancer, dementia, hypertension)
- **Induce infectious diseases** (HIV, HCV)
- **Affect the efficacy of prescribed medications**
- Be associated with **abuse of Rx medications**
- Result in **low birth weight**, premature deliveries, developmental delays
- Result in **addiction**
How is substance abuse relevant to primary care?

Higher Prevalence of Medical Conditions in Substance Abusers vs. Controls

Physicians Can Play a Role in Both Prevention and Treatment
Projected Prescriptions for Hydrocodone and Oxycodone Products Dispensed by US Retail Pharmacies, Years 1991–2008

Source: SDI Health Vector One© National (VONA)
Source of Prescription Narcotics among Those Who Used in the Past Year, 12th Grade*

* Categories are not mutually exclusive

SOURCE: University of Michigan, 2010 Monitoring the Future Study
New vs. Continuing or Switch/Add-on Opioid Prescriptions Dispensed by US Retail Pharmacies as a Function of Specialty, 2009

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Physicians can also play a role in Treatment

- In Specialty Treatment - 2,600,000
- Abuse/Dependent - 22,500,000
- Harmful Users - ?
Physicians Can Play a Role in Treatment

- Most substance abusing patients don’t feel they need treatment and therefore won’t seek it on their own.
<table>
<thead>
<tr>
<th>Treatment Referral Sources</th>
<th>1990</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criminal Justice</td>
<td>38%</td>
<td>59%</td>
</tr>
<tr>
<td>Employers/EAP</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Welfare</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>Hosp/Phys</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Evidence for SBIRT in primary care

- Using screening and brief intervention (SBI) procedures in general medical settings can make a difference in drug use behaviors
  - Research has demonstrated that SBI can reduce alcohol and tobacco use.

Tobacco - USPSTF Grade A (strongly recommended)
http://www.uspreventiveservicestaskforce.org/uspstf/uspsbac.htm

Alcohol - USPSTF Grade B (recommended)
http://www.uspreventiveservicestaskforce.org/uspstf/uspsdrin.htm
Evidence for SBIRT in primary care

Illicit Drugs: Promising and Proliferating

- Bernstein, et al. 2005: Randomized Controlled Trial (RCT)
- WHO study, 2008: Randomized Controlled Trial (RCT) in Multiple Sites Internationally
- InSight Project Research Group 2009
- Madras, et al. 2009: SAMHSA program evaluation of (SBIRT) for illicit drug and alcohol use at multiple sites
SBIRT Reduces Heavy Alcohol and Drug Use in a Hospital District-Based Program (N=1,278)

Source: The InSight Project Research Group, 2009. Alcoholism: Clinical and Experimental Research

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SAMHSA SBIRT Service Program - Reductions in Substance Use at 6 Month Follow-up

Source: Madras et al., 2008 Drug and Alcohol Dependence
Physicians can:

- Identify patients at high risk for a substance use disorder and refer for specialty assessment and treatment, if necessary.

- Identify those at lower or moderate risk to intervene early and prevent the escalation to abuse and addiction.
Physicians Don’t Routinely Screen for Substance Abuse – Why?

• Don’t believe it is a medical problem
• Don’t believe there is effective treatment
• Can’t be reimbursed
• Don’t know what to do
• Not enough time
Physicians Say They Don’t Know What To Do

• National surveys of medical schools suggest dramatic variability in training in this area.
  • More than 55 percent of medical students had 9 hours or less of formal instruction on substance abuse (n=1340)

• Residency training
  • Only about half of residency programs required a curriculum in substance use disorders
  • 65 percent of residents had 9 hours or less of formal instruction on substance abuse (n=246)

Source: Yoast et al., 2008. Journal of Addictive Diseases; NIDA CoE Formative Assessment
Centers of Excellence for Physician Information

NIDA has partnered with the American Medical Association and eight medical schools across the country to develop curriculum resources that contain scientifically accurate information about substance abuse and addiction.

These curriculum resources address pressing issues facing physicians today, in particular recognizing risk factors for as well as identifying prescription drug abuse in their patients.

www.drugabuse.gov/coe
The Addiction Performance Project offers healthcare providers the opportunity to help break down the stigma associated with addiction and promote a healthy dialogue that fosters compassion, cooperation, and understanding for patients living with this disease.

Dramatic reading by award-winning professional actors followed by a brief expert panel reaction and facilitated audience discussion of:

- the challenges and opportunities in caring for drug-addicted patients in primary care settings,
- physician biases, and
- how best to incorporate screening, brief intervention, and referral to treatment into primary care settings.
**NIDAMED** Online Screening Tool

- **NIDA Quick Screen**
- **NMASSIST - Based on the WHO ASSIST**
- Screens for tobacco, alcohol, illicit, and non-medical prescription drug use
- Based on patients' responses, automatically:
  - Leads to next appropriate question
  - Determines substance involvement score (i.e., risk level not a diagnosis)
- Links to additional resources

**Website and Online Tool**
Online Resource Guide

- Rationale
- Instructions on how to implement screening
- The five A’s of intervention – Ask, Advise, Assess, Assist, Arrange
- Scripts on how to discuss drug use with patients
- Additional Resources
Quick Reference Guide

- Drug listing outlining the different classes
- Screening questions
- Point value for each response
- Brief summary of the recommended intervention for each risk level
• A free, nationwide service to help primary care providers seeking to identify and advise their patients regarding alcohol and drug abuse before they evolve into life-threatening conditions.

• PCSS-P provides physicians with easy access to clinical tools (e.g., NIDA Screening Tool), information, and resources to help them incorporate screening, brief intervention, and referral to substance abuse treatment into their practices.

• PCSS-P also links physicians to trained clinical advisors that can provide telephone or email responses to specific questions, and offer support on how to use and integrate PCSS-related clinical resources as a regular part of patient care.

• For more information, please visit PCSS-P at www.PCSSmentor.org, email PCSSproject@asam.org or call 1-877-630-8812.
Encouraging Patients to Talk About Drug Use

Without the whole picture, you might not get the whole treatment.

To give you the best possible care, your doctor needs to know about any and all drugs you are taking, including tobacco, alcohol, illicit drugs, over-the-counter and prescription medications—even those not prescribed for you.

Tell Your Doctor About ALL the Drugs You Use.
www.drugabuse.gov/nidamed
Encouraging Patients to Talk About Drug Use
The Ultimate Goal – Addressing substance abuse becomes a part of routine medical care.

• Practicing physicians need to implement

• It must become a routine part of medical education.