

OFFICE OF
DEPUTY ASSISTANT SECRETARY FOR LEGISLATION (HEALTH)
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

September 25, 1970

John --

Attached is backup material and a page on the major issues with regard to communicable diseases.

The enrolled bill will likely be to the President within 10 days.

A handwritten signature in dark ink, appearing to read 'Glen Wegner', with a stylized, cursive script.

Glen Wegner

Attachments

September 28, 1970

MEMORANDUM FOR KEN COLE

Attached is additional material on the Communicable Disease Control Act of 1970 which I am forwarding as per our earlier conversation on this subject.

JOHN DEAN

MEMORANDUM

THE WHITE HOUSE

WASHINGTON

September 17, 1970

*See
mag*

MEMORANDUM FOR MR. MAGRUDER

FROM: MARGITA WHITE *M.W.*

RE: Librium-Valium Article

Herb recommended against planting the Librium-Valium article as an editorial or with a columnist. He suggested instead that Nofziger arrange to have it inserted in the record. Nofziger gave it to Hartmann who requested Rep. Springer (Ill.) to insert it. Springer objected because this would foul up their current strategy, which is to let the bill go to the floor without a change and then offer an amendment to insert these drugs on the floor.



UNITED STATES DEPARTMENT OF JUSTICE

BUREAU OF NARCOTICS AND DANGEROUS DRUGS
WASHINGTON, D.C. 20537

Tentative Schedules for Seminars

Nov. 18	Hawaii	2 seminars
Nov. 20	Guam	2 seminars
Nov. 23	Osan A.F.B. Korea	1 seminar
Nov. 24	Seoul area	2 seminars
Nov. 25	Tachikawa AFB Japan	2 seminars
Nov. 27	Yokota AFB Japan	2 seminars
Nov. 30	Okinawa	2 seminars
Dec. 1-2	Clark AFB Phillipines	1 seminar each day
Dec. 3	Yokosuka Japan	1 seminar

BUREAU OF NARCOTICS AND DANGEROUS DRUGS
UNITED STATES DEPARTMENT OF JUSTICE
MILITARY SCHOOL No. 9
Nov 23rd - Dec 4th, 1970
TOKYO, JAPAN

MONDAY - November 23, 1970

8:30 - 9:00 REGISTRATION

9:00 - 9:15 WELCOME

• Mr. Frank Bartimo
Assistant General Counsel (M & RA)
Department of Defense

• Mr. Perry Rivkind
Assistant Director for Training
Bureau of Narcotics and Dangerous Drugs
Department of Justice

9:15 - 9:30 ORIENTATION

• Special Agent James J. McMahon
Staff Training Instructor
Bureau of Narcotics and Dangerous Drugs
Department of Justice

9:30 - 10:45 THE MILITARY DRUG PROBLEM

• Mr. Frank Bartimo
• Colonel E. G. Hopson
United States Air Force
Executive Officer
Department of Defense
Drug Abuse Control Committee

10:45 - 1:00 HISTORY OF THE NATIONAL & INTERNATIONAL DRUG TRAFFIC

• Special Agent Robert M. Stutman
Training and Prevention Officer
Bureau of Narcotics and Dangerous Drugs
Department of Justice

1:00 - 2:00 LUNCH

2:00 - 3:00 BNDD ORGANIZATION, FUNCTIONS & POLICY

Mr. Perry A. Rivkind
Assistant Director for Training
Bureau of Narcotics and Dangerous
Drugs
Washington, D. C.

3:00 - 4:00 NARCOTICS TRAFFIC IN THE FAR EAST

• Special Agent Rustam Aruslan
Special Agent in Charge
Bureau of Narcotics and Dangerous Drugs
Department of Justice
Tokyo District Office
Tokyo, Japan

4:00 - 5:30 RECOGNIZING A DRUG ABUSER

• Special Agent Joseph J. Catale
Training and Prevention Officer
Bureau of Narcotics and Dangerous Drugs
Department of Justice

TUESDAY - November 24, 1970

9:00 - 9:30 FILM: "NARCOTICS AND THE LAW"

9:30 - 12:30 PHARMACOLOGICAL & PHYSIOLOGICAL EFFECTS OF DRUG
ABUSE & THE INVESTIGATION OF A DRUG-CAUSED DEATH

• Lieutenant Colonel R. C. Froede, M.D.
Armed Forces Institute of Pathology
Forensic Pathology Branch
Washington, D.C.

12:30 - 1:30 LUNCH

1:30 - 5:00 DRUG IDENTIFICATION PART I
OPIATES, SYNTHETICS & COCAINE

• Special Agent James J. McMahon

5:00 - 5:30 FILM: "ADDICTS TAKING SHOTS"

WEDNESDAY - November 25, 1970

9:00 - 9:30 FILM: "THE RIDDLE"

9:30 - 12:00 UNIFORM CODE OF MILITARY JUSTICE & THE TRIAL OF
DRUG CASES

• Mr. Michael R. Sonnenreich
Deputy Chief Counsel
Bureau of Narcotics and Dangerous Drugs
Department of Justice

12:00 - 1:00 INITIATION & DEVELOPEMENT OF A DRUG CASE

• Special Agent Gabriel Dukas
Staff Assistant
Office of Criminal Investigations
Bureau of Narcotics and Dangerous Drugs
Department of Justice

1:00 - 2:00 LUNCH

2:00 - 5:00 DRUG IDENTIFICATION PART II
BARBITURATES & AMPHETAMINES

• Mr. Edwin C. Turner
Educational Program Specialist
Office for Science & Drug Abuse Prevention
Bureau of Narcotics and Dangerous Drugs
Department of Justice

5:00 - 5:30 FILM: "THE SPEED SCENE - PROBLEMS OF
AMPHETAMINE ABUSE"

THURSDAY - November 26, 1970

9:00 - 5:30 THANKSGIVING DAY -- HOLIDAY

FRIDAY - November 27, 1970

9:00 - 9:30 FILM: "BEYOND 1SD"

9:30 - 12:30 UNDERCOVER TECHNIQUES
 . Special Agent Gabriel Duka
12:30 - 1:30 LUNCH
1:30 - 4:00 DRUG IDENTIFICATION PART III
 HALLUCINOGENS & PSYCHOTOMIETICS
 . Mr. Edwin C. Turner
4:00 - 5:00 DRUG CONCEALMENT
 . Special Agent Joseph J. Catale
5:00 - 5:30 FILM: "DRUGS AND THE NERVOUS SYSTEM"

SATURDAY & SUNDAY - November 28 & 29, 1970

9:00 - 5:30 OFF

MONDAY - NOVEMBER 30, 1970

9:00 - 9:30 FILM: "INSIGHT OR INSANITY"
9:30 - 10:30 CLANDESTINE LABORATORIES
 . Special Agent Joseph J. Catale
10:30 - 12:00 PSYCHOLOGY OF DRUG ABUSE
 . Special Agent Robert M. Stutman
12:00 - 1:00 LUNCH
1:00 - 2:00 NON-CONTROLLED SUBSTANCES OF ABUSE
 . Special Agent Michael J. Costello
2:00 - 5:00 INFORMERS & INFORMANT DEVELOPEMENT
 . Special Agent Gabriel Duka

5:00 - 5:30 FILM: "STAY ALERT -- STAY ALIVE"

TUESDAY - December 1, 1970

9:00 - 9:30 FILM: "THE DISTANT DRUMMER"

9:30 - 11:00 ARREST, SEARCH & MILITARY SEIZURE PROCEDURES

. Mr. Michael R. Sonnenreich

11:00 - 12:00 NEW FEDERAL DRUG LAWS AND ITS IMPACT ON
THE MILITARY

. Mr. Michael R. Sonnenreich

12:00 - 1:00 LUNCH

1:00 - 5:00 DRUG IDENTIFICATION PART IV
MARIHUANA

. Special Agent James J. McMahon
. Mr. Edwin C. Turner

5:00 - 5:30 FILM: "MARIHUANA"

WEDNESDAY - December 2, 1970

9:00 - 9:30 DRUG INTERACTION

. Lieutenant Colonel Richard C. Froede, M.D.

9:30 - 5:30 SURVEILLANCE

. Special Agents James J. McMahon
Joseph J. Catalo
Michael P. Costello
Gabriel Dukas
Robert M. Stutsman

FILM: "SURVEILLANCE"

THURSDAY - December 3, 1970

9:00	-	9:30	FILM: "THAILAND EXECUTION"
9:30	-	10:30	FRADULENT & DECEPTIVE PRACTICES
			. Mr. Edwin C. Turner
10:30	-	12:30	COMPLIANCE INVESTIGATIONS
			. Special Agent Michael P. Costello
12:30	-	1:30	LUNCH
1:30	-	3:00	CURRENT LEGAL TRENDS
			. Mr. Michael R. Sonnenreich
3:00	-	4:00	EVIDENCE HANDLING
			. Special Agent Joseph J. Catale
4:00	-	5:00	LOCAL PROBLEMS
			. Class Participation
5:00	-	5:30	COURSE REVIEW & CRITIQUE

FRIDAY - December 4, 1970

9:00	-	11:30	FINAL EXAMINATION
11:30	-	2:00	RECEPTION, GRADUATION LUNCHEON & AWARDING OF CERTIFICATES

THE WHITE HOUSE
WASHINGTON

9-18-70

John Dean,

Although it is
No. - these were
Wally's suggestions.

Nidecker

September 17, 1970

MEMORANDUM FOR: William E. Timmons
Assistant to the President

FROM: Wallace H. Johnson
Associate Deputy Attorney General

SUBJECT: Suggested Invitees to Signing
Ceremony on Legislation Affording
D.C. A Non-voting Delegate in the
House of Representatives (H.R.
18725)

If a signing ceremony is to be held with respect to the subject legislation, the persons listed below should be considered when invitations are extended.

I have designated with an asterisk those about whom there may be some sensitivity, which should be kept in mind when the final invitee list is compiled. A "+" indicates persons who have been particularly active and worked particularly hard on this issue.

Legislative Branch

a. *Senate District Committee

Joseph D. Tydings
Alan Bible
+William B. Spong
Thomas F. Eagleton

+Winston L. Prouty
Charles E. Goodell
+Charles McC. Mathias, Jr.

b. * House District Committee

John L. McMillan
Thomas G. Abernethy
William L. Dawson

+Ancher Nelsen
William L. Springer
Alvin E. O'Konski

House District Committee (Cont'd.)

John Dowdy
+Charles C. Diggs, Jr.
G. Elliott Hagan
Don Fuqua
+Donald M. Fraser
+Brock Adams
Andrew Jacobs, Jr.
Peter N. Kyros
William L. Hungate
Earle Cabell
Ray Blanton

William H. Harsha
Joel T. Broyhill
Larry Winn, Jr.
Gilbert Gude
+Lawrence J. Hogan
Vernon W. Thomson
+Henry P. Smith, III
Earle F. Landgrebe

c. Other Senators

Mike Mansfield
Hugh Scott

d. Other Representatives

John W. McCormack
Carl Albert
Gerald R. Ford

e. * Legislative Branch Staff Personnel

*John T. McEvoy, Staff Director, Senate District Committee
Wesley Williams, Counsel, Senate District Committee
*James T. Clark, Clerk, House District Committee
*John Hogan, Minority Clerk, House District Committee
*Hayden Garba, Staff Director, House District Committee
*Jaques DuPuy, Office of Congressman Brock Adams

f. Justice Department

John N. Mitchell
Richard G. Kleindienst
Wallace H. Johnson
Donald E. Santarelli
William H. Rehnquist
Herbert E. Hoffman
John T. Tansey
+Nathan Siegel

g. D.C. Government

Walter E. Washington, Commissioner
Graham W. Watt, Deputy Commissioner

D.C. Council:

Gilbert Hahn, Jr., Chairman
Sterling Tucker, Vice-Chairman
Stanley J. Anderson, Member
Philip J. Dougherty, Member
Margaret A. Haywood, Member
Rev. J. A. Moore, Jr., Member
Rev. Carleton W. Veazey, Member
Dr. Henry S. Robinson, Member
Joseph P. Yeldell, Member

Charles T. Duncan, Director of Public Safety
Hubert B. Pair, Acting Corporation Counsel
Robert Kneipp, Assistant Corporation Counsel

h. D.C. Board of Elections

J. E. Bindeman, Chairman
Robert Martian, Member
Charles Fisher, Member
William H. Huey, Executive Secretary

i. Political Parties

Carl L. Shipley, Republican National Committeeman
Mrs. J. Willard Marriott, Republican National Committeewoman
*Rev. Channing Phillips, Democratic National Committeeman
*Miss Flaxie Pinkett, Democratic National Committeewoman
Edmund E. Pendleton, Jr., Chairman, D.C. Republican Committee
*Bruce L. Ferris, D.C. Democratic Committee Chairman

j. Others

*David Carliner, Chairman, Washington Home Rule Committee
Jack Nevius, Vice Chairman, Washington Home Rule Committee
Mrs. Phillip G. Fortune, League of Women Voters
**Simon L. Cain, President, Federation of Civic Associations
**Donald R. Crone, President of the Federation of Citizens Associations

** I know nothing about these people but the organizations would seem to be appropriate for representation at the signing.

***Sturgis Warner, practicing attorney and Consultant to the D.C. Board of Elections (this man has been the principal moving force behind this legislation for many years)

*Herbert J. Miller, President, D.C. Bar Association

*Bruce Harrison, President, Washington Bar Association

Thomas M. Walsh, President, Metropolitan Washington Board of Trade

President of the Washington Chamber of Commerce

For your information, the following Members of the Congress have sponsored representation legislation or constitutional amendments in the 91st Congress:

House Democrats

Fraser
Adams
Diggs
Jacobs
Kyros
Abernethy
Cabell
Hungate
Giaimo
Conyers
Celler
Corman
Udall

House Republicans

Nelsen
O'Konski
Winn
Zwack
Gude
Ford (Mich.)
Springer
Harsha
Horton
Steiger (Ariz.)
May (Wash.)
Hogan
Quie
Thomson (Wis.)
Smith (N.Y.)
Landgrebe
Anderson (Ill.)
Biester
Button
Clausen, (Calif.)
Erlenborn
Frelinghuysen
Halpern
McDade
Morse

House Republicans (Cont'd.)

Stafford
Vander Jagt
Connable
Heckler (Mass.)
McClory
Reid (N.Y.)
Dellenback
Hastings
McCloskey
Riegle
Ruppe
Esch
Robison
Eshleman
Pollock
Brotzman
Buchanan
Broyhill (Va.)
Wiggins
Bell (Calif.)

Senate Democrats

Bayh
Bible
Harris
Hart
Hartke
Hughes
Inouye
Kennedy
McGee
Mondale
Montoya
Muskie
Nelson
Pell
Proxmire
Randolph
Ribicoff
Tydings

Senate Republicans

Hatfield
Goodell

September 4, 1970

MEMORANDUM FOR BILL CASSEIMAN

I would certainly like to review the material Wally Johnson prepares for you in response to your memo of August 25, 1970 re a signing ceremony for the drug bill.

Thank you.

JOHN DEAN



flc

August 27

John —

I don't know whether
Wally has had a chance
to mention this to you.

We have asked BNDD
for their recommendations.

Alan

THE WHITE HOUSE
WASHINGTON

August 25, 1970

MEMORANDUM FOR WALLACE H. JOHNSON
Associate Deputy Attorney General
Department of Justice

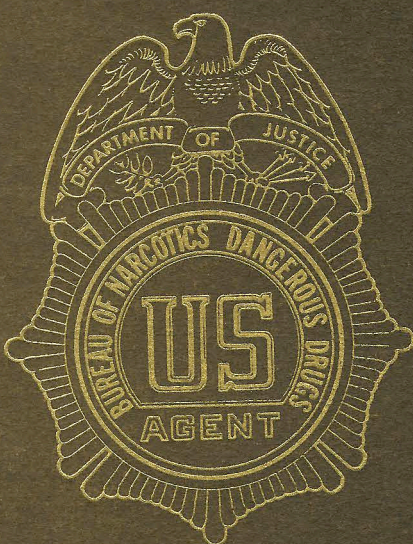
Per our earlier discussions on the subject, will you please put together a brief scenario (suggested invitees, location, remarks, etc.) for a signing ceremony on the drug bill.

Thanks, Wally.

A handwritten signature in black ink, appearing to read 'W. E. Casselman, II', with a large, stylized loop at the end.

William E. Casselman, II
Deputy Special Assistant to
the President

SPECIAL AGENT GRADUATION



PROGRAM

Musical Selections
U.S. Army Band

National Anthem

Invocation

Welcome

Perry A. Rivkind
Assistant Director for Training
BNDD

Introductions

John E. Ingersoll, Director
BNDD

Address

Honorable John W. Dean III
Counsel to the President

Special Awards Presentations

John E. Ingersoll

Presentation of Certificates

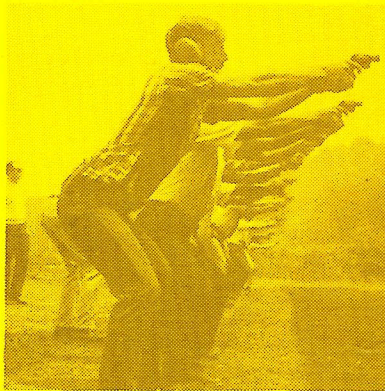
John E. Ingersoll

Closing Musical Selection

... You men will have to
extend yourselves
to the utmost, perhaps beyond
what you now think you
are capable of doing
until the reinforcements arrive.
You men are a special
group, a different group.
You have unique skills.
You have unique characteristics.
You have unique challenges
and opportunities. You belong to
what is going to be *the* elite federal
enforcement agency.
I want each of you to become
leaders, not only in this agency,
but in this nation's fight against the
depredation of drug abuse. . .

Remarks by Director, John E. Ingersoll
at the first BNDD Special Agents
Graduating Class





SPECIAL AGENT BASIC TRAINING CLASS NUMBER 10

Donald Abrams
 Ramon Benavides, Jr.
 Fredric D. Boff
 Christopher M. Bradley
 Louis T. Candell
 Lloyd N. Clifton
 George M. Feeney
 John E. Fencer, Jr.
 Joseph E. Fortier, III
 James F. Glauner, III
 Ronald Gospodarek
 Eino B. Hella
 George E. Hoelker
 Peter M. Johnson
 Douglas W. Kuehl
 Joaquin Legarreta, Jr.

Robert E. Lumsden, Jr.
 Nile W. McDonald
 Ed F. McCravy
 Alvin C. Overbaugh
 Armando Ramirez
 Jerry A. Rinehart
 Ruben Salinas
 Melvin O. Schabillion
 Jerold W. Schubel
 Dorsey L. Shannon, Jr.
 Thomas J. Stacy
 Ernest D. Strange
 Richard D. Waber
 Thomas H. Walters
 Daniel H. Wedeman
 Robert W. White

**Special Agent
Training Division**

Ernest J. Marquardt, Chief

Class Coordinator

Willard W. Rutledge

Class Counselors

James Hilbert
James Rose
Robert Voorhees

BUREAU
OF
NARCOTICS
AND
DANGEROUS
DRUGS
US
DEPARTMENT
OF
JUSTICE

CHARLES E. WIGGINS
25TH DISTRICT, CALIFORNIA

COMMITTEE:
JUDICIARY

SUBCOMMITTEE:
BANKRUPTCY AND
REORGANIZATION

SELECT COMMITTEE
ON CRIME

Congress of the United States
House of Representatives
Washington, D.C. 20515

September 15, 1970

1114 LONGWORTH
HOUSE OFFICE BUILDING
WASHINGTON, D.C. 20515
202-225-4111

DISTRICT OFFICES:
CROWN BUILDING
11001 VALLEY MALL
SUITE 202
EL MONTE, CALIFORNIA 91731
213-442-5726

BRASHEARS CENTER
SUITE 625
1400 NORTH HARBOR BOULEVARD
FULLERTON, CALIFORNIA 92632
714-879-2542

Mr. John Dean
Counsel to the President
The White House
Washington, D. C.

Dear John:

Enclosed is the text of the amendment which will be offered by Congressman Pepper to H. R. 18583, the Comprehensive Drug Abuse Prevention and Control Act of 1970.

In essence, the amendment simply reschedules amphetamines and subjects them to the production controls available in the case of Schedule I and II drugs.

I am informed that the "Dear Colleague" letter, a copy of which is also enclosed, has elicited a favorable response to date from approximately 12 Members.

Congressman Pepper is also considering an amendment which would condition the right to bail in major narcotics cases to an agreement to be tried in absentia if the defendant fails to appear for trial. This would doubtless open a can of worms and Claude is being urged to refrain from offering such an amendment. The proposal, however, is in response to the very real problem of major heroin importers regularly jumping bail in the New York area.

I am aware of the opposition to production controls for amphetamines by industry representatives, and perhaps by Justice and HEW as well. A good case can be made for such controls, however, and I suggest that it would not be wise for the Administration to take a public position on this question. It would be prudent, in my opinion, for the House to work its will without a White House position being declared. If serious Administration opposition exists, I am sure that the conferees will give proper weight to the Administration's position.

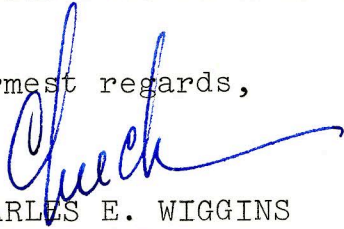
Mr. John Dean

-2-

September 15, 1970

If I can be of further assistance on this legislation,
please give me a call.

Warmest regards,



CHARLES E. WIGGINS
Member of Congress

CEW:gl
enclosures

BOOKS

Kaplan, John.
THE NEW PROHIBITION.
I don't know publisher, etc.

Camage, J. R., & Zerkin, E. L.
MARIHUANA: AN ANNOTATED GUIDE: A COMPREHENSIVE GUIDE TO THE ENGLISH-LANGUAGE
LITERATURE ON CANNABIS (MARIHUANA). 280p. Literature from 1842 to 1969.
Stash Press, 638 Pleasant St., Beloit, Wisc., 53511 \$5.95

I think Goode, Erich, has a book on marihuana. and another to come out soon
called The Marihuana Smokers. Ask R. Wolpe, librarian.

g. leary
8/27/70

*file
marihuana*

Esterase Activity of Chymotrypsin on O-DNP-L-Tyrosine Ethyl Ester Substrates

While developing a chemical method for the assay of ACTH by dinitrophenylation and subsequent hydrolysis with chymotrypsin, we observed that no di-DNP-seryl-tyrosine could be identified in the digestion mixture by gel filtration on 'Sephadex G-25' column and thin layer chromatography. This suggested that DNP-ACTH is attacked by the enzyme, not at the tyrosyl-2 peptide bond, but at other positions yielding large peptide fragments. The O-DNP derivative of tyrosine may interfere with the action of chymotrypsin on the tyrosyl peptide bond. No work seems to have been reported on the esterase activity of chymotrypsin when the phenolic group of tyrosine is blocked by alkylation or acylation. To verify our hypothesis, model substrates were synthesized in which the phenolic group of tyrosine was blocked by a DNP residue.

N-Acetyl-O-DNP-L-tyrosine ethyl ester was synthesized from N-acetyl-L-tyrosine ethyl ester by Sanger's reagent. A colourless crystalline solid was obtained after recrystallization from aqueous ethanol and had the following characteristics: m.p. 113°-114° C; infrared absorbance peaks, in cm^{-1} (KBr): 1,730, 1,740 (carbonyl); 1,650, 1,600 (amide); 1,560, 1,350, 850 (nitro); found C, 54.46; H, 4.44; N, 9.88— $\text{C}_{19}\text{H}_{19}\text{O}_8\text{N}_3$ requires C, 54.67; H, 4.58; N, 10.06 per cent. No hydrolysis of this substrate with chymotrypsin could be detected by a potentiometric method, even after incubation for 12 h, while the corresponding free phenolic compound is the usual substrate for chymotrypsin with a K_m value of 6.9×10^{-4} M (ref. 1).

Because this substrate was sparingly soluble in aqueous medium, further evidence was sought by synthesizing a soluble substrate, N-maleyl-O-DNP-L-tyrosine ethyl ester. N-maleyl-L-tyrosine ethyl ester was synthesized by maleylation of L-tyrosine ethyl ester using the procedure of Sheehan *et al.*² An oily product was obtained which could not be crystallized, but which was purified by high voltage electrophoresis in a buffer of pyridine-acetic acid-water (25:1:225, pH 6.5), at a voltage of 2 kV for 1.5 h. The pure maleyl derivative was eluted from the paper with acetone yielding an oily material. Its purity was checked by high voltage electrophoresis and thin layer chromatography. This material was directly dinitrophenylated in the usual way giving a colourless solid: m.p. 58°-60° (decomp.); infrared absorbance, in cm^{-1} (KBr) 1,720, 1,740 (carbonyl); 1,650, 1,600 (amide); 1,560, 1,345, 850 (nitro); found C, 53.03; H, 4.40; N, 8.43— $\text{C}_{21}\text{H}_{19}\text{O}_{10}\text{N}_3$ requires C, 53.28; H, 4.02; N, 8.87 per cent. N-Maleyl-L-tyrosine ethyl ester was easily cleaved by chymotrypsin (K_m , 2.08×10^{-3} M), but the corresponding O-DNP derivative resisted hydrolysis.

These experiments strongly suggest that, for chymotryptic cleavage at the tyrosyl bond, the phenolic group must be free. It would be interesting to test model substrates in which the DNP group was replaced by groups having a negative inductive effect with varying degrees of hindrance.

This research was supported in part by a research grant from the US National Science Foundation. We thank Dr W. R. Slaunwhite for advice and Mrs L. Emerson and Mr F. Maenza for assistance.

N. KUNDU
SUJATA ROY

Medical Foundation of Buffalo,
73 High Street,
Buffalo, New York 14203.

Received March 16, 1970.

Marijuana and Immediate Memory

CLINICAL anecdotes and recent studies suggest that a marijuana "high" interferes with immediate memory (ref. 1, and unpublished manuscripts by L. Clark and A. Wikler). We describe here the effects of calibrated amounts of tetrahydrocannabinol (THC) on cognitive tasks which require immediate memory.

We used THC that had been extracted from marijuana supplied by the Bureau of Narcotics and Dangerous Drugs. Thin layer and gas liquid chromatography of these extracts showed predominantly 1- Δ^1 -THC, with some cannabidiol and cannabinol. Quantitative calibrations were made so that doses (20, 40 and 60 mg) were based on the actual content of 1- Δ^1 -THC. The doses were in the range which, for synthetic 1- Δ^1 -THC administered orally, invariably produces clinical effects approaching those of psychotomimetic drugs, such as lysergide^{2,3}. A placebo was composed from an extract of marijuana with cannabinoids removed.

The subjects, who were fasting, received their doses in a randomized order unknown either to them or to the testers. Four oral doses, in 95 per cent ethanol diluted with water, were given on four separate experimental days at least one week apart. The eight subjects were college-educated males in their twenties, weighing between 63 and 85 kg, who had been screened for good physical and mental health. All had smoked marijuana, but at no greater frequency than once a month. They were tested before the drug was given, and at 1.5, 3.5 and 5.5 h afterwards. All testing was done individually in an austere research laboratory.

The digit span task required subjects to repeat, either forwards or backwards, a series of random digits read by the experimenter at a rate of one a second. The span was the longest number of digits that could be reproduced without error on two successive test trials. If the subject's attention waned, the investigator restarted the trial to determine accurately the upper limit of the subject's capacity for that test period.

Table 1. DIGIT SPAN AND THC DOSES TESTED BY ANALYSIS OF VARIANCE (d.f. = 3,21).

THC dose	Means	
	Digits forward	Digits backward
Placebo	9.0	7.8
20 mg	8.2*	6.9*
40 mg	8.1*	6.6*
60 mg	7.9*	6.4*
F	4.5	5.2
Significant	P < 0.05	
	P < 0.01	

* These values significantly differ from placebo at P < 0.01 by t-test for correlative means, 2-tail.

Table 1 shows that significant differences between placebo and each of the THC doses were obtained for both forward and backward digit spans. There were, however, no significant differences between effects of 20, 40 and 60 mg doses, indicating that the smaller dose of THC impairs immediate memory and that larger doses do not significantly augment the impairment. The most significant decrement in forward memory occurred 1.5 h after drug ingestion, with a return almost to the pre-administration result at 3.5 h. For backward memory, there was a greater mean decrement over doses and the impairment was still present 3.5 h after ingestion.

We also gave three subjects a more complicated digit reordering test, in two stages. We first read a list of random digits, shorter by two numbers than the subject's forward memory span before he had taken the drug that day, and asked him to recite the digits in the same order. We then instructed the subject to arrange the digits in serial rank order, either upwards or downwards. Each of the three subjects was given at least two reordering tasks during the four testing periods of each experi-

forty trials. In the drug state (1.5 and 3.5 h after ingestion for all doses), they made forty-eight errors in thirty-five trials. This difference between the total number of drug and non-drug errors was significant (Mann-Whitney Test).

In the non-drug state, all nineteen errors involved the omission of a given digit or the insertion of one not given. In the drug state, there were thirty-seven errors of this type. In the drug state only, there were also eleven errors in which the subject did not carry out instructions given a few seconds before: for example, he would reorder from low to high rather than follow the instructions to reorder from high to low.

Our observations, like those of others⁴, indicate that impairments in immediate memory from marijuana intoxication do not follow a smooth time-function but, rather, are episodic, brief in duration and not always under volitional control. These episodes often interrupted the speech patterns of our subjects and seemed to be associated with the intrusion of extraneous perceptions and thoughts (compare ref. 5). One subject commented: "Well, I just felt very confident and able to remember the numbers . . . then when it came time to give them back, I'd see and hear, mostly see, I think, all kinds of numbers. And I wouldn't know which ones were the right ones." Another subject commented: "I can understand what I'm thinking, but I can't understand what I'm saying. . . . Because there are so many thoughts in between what I'm saying . . .".

The cognitive impairments induced by THC also involve intermittent lapses in attention. One subject stated: "Everything's pretty mixed up . . . I lose track of what's been happening. And it sometimes even seems like a long time has passed, but I know it hasn't, because I'm generally still in the middle of a word or sentence". Because we exhorted our subjects to try as hard as possible, we feel that they were able considerably to mitigate the influence of impaired attention on their cognitive performance. Usually the cognitive changes abated in 3 to 5 h, although some subjects described residual impairment up to 24 h later.

Similar intermittent defects in remembering relevant events may contribute to various types of behavioural disorders, including acute psychoses^{6,7}. Elsewhere, we discuss correlations between THC-induced impairments in immediate memory and other behavioural changes⁸.

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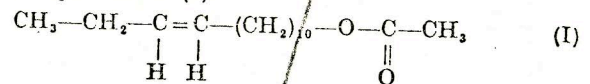
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Sex Pheromone of the Oblique-banded Leaf Roller Moth

ALTHOUGH at least ten pheromone compounds have been reported for lepidopterous species, only three¹⁻³ have proved to be true sex attractants in natural field conditions. We now report that the structure of the sex attractant of the oblique-banded leaf roller *Choristoneura rosaceana* (Lepidoptera, Tortricidae), one of the most widely distributed North American tortricids, is *cis*-11-tetradecenyl acetate (I).



Two years ago, after identifying the sex attractant of the red-banded leaf roller moth (*Argyrotaenia velutinana*) as (I), we trapped many oblique-banded leaf roller males along with red-banded leaf roller males in orchard traps baited with this compound. We established a laboratory rearing programme for oblique-banded leaf rollers and processed 20,000 female abdominal tips as before^{2,3}. At least a hundred-fold increase in free attractant was obtained by saponification of the crude extract followed by acetylation. Identification of the active component was accomplished by the usual techniques^{2,3} of column, gas and thin-layer chromatography, ozonolysis and mass spectrometry.

Synthetic compound (I) was very stimulatory to males in the laboratory and has attracted hundreds of oblique-banded leaf roller males in field trapping experiments in the past two years. The *trans* isomer also elicited a response in laboratory bioassays until it was fractionated twice on silver nitrate-impregnated silica gel thin-layer plates to remove traces of the *cis* isomer (I), as was the case for the false codling moth⁴. The *trans* isomer had no inhibitory or masking effects in the laboratory bioassay, but was found to be a very potent inhibitor to male response in the field when added in low percentages to the attractant (I). This emphasizes the importance of field bioassays for biological activities which are not evident in the laboratory.

Because both oblique-banded and red-banded leaf roller males are attracted to the same compound in the field, it is not clear how specificity is effected. The two species have overlapping seasonal and diurnal cycles and share the same host plants. The addition of dodecyl acetate to (I) does effect partial reproductive isolation by drastically increasing attractancy for red-banded leaf roller males⁵ and decreasing it for oblique-banded leaf roller males. Preliminary studies indicate that other compounds can give the opposite effect when added to (I) in enhancing oblique-banded leaf roller attractancy and inhibiting red-banded leaf roller response. The emission of different secondary compounds by females of each species along with the sex attractant (I) could effect reproductive isolation in the field for these two species.

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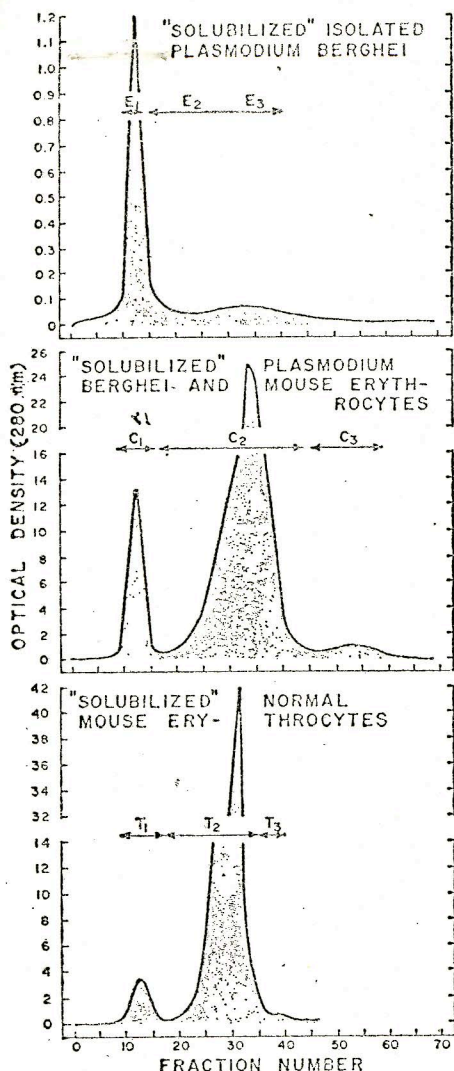


Fig. 1. Optical density (280 nm) of plasmodial fractions. (Top) Free plasmodia and plasmodial fragments; (center) infected mouse red blood cells; and (bottom) normal mouse red blood cells.

Preparations A, B, C, and D and preparations R, S, and T were each injected into a group of mice. Representative fractions from various portions of each Sephadex G-200 peak for each fractionated preparation were pooled, and each pooled sample was injected into its respective group of mice. Each mouse received a single intraperitoneal injection of 1 ml of its respective preparation. All preparations were injected as freshly obtained and proved to be noninfective. All mice were from 6 to 7 weeks of age at the time of injection.

Fifteen weeks later, the animals were challenged intraperitoneally with 10×10^6 mouse cells infected with *P. berghei* NK65D. Three major infection responses were exhibited. The weekly composite mean percentage parasitemias for mice exhibiting each type of

response appear in Table 1. Protected mice responded with transient low parasitemias, rapid disease resolution, and high survival rates (PS). Unprotected mice responded with severe protracted parasitemias, a high mortality rate (NS), and a few eventual spontaneous recoveries (NPS). These responses conform to those reported (4, 7, 8) for protected and variously treated or nontreated unprotected control A/J mice.

The protective response (PS) was limited to animals receiving crude plasmodial preparation A, B, C, D and partially purified plasmodial fractions C_1 and E_1 . Of a total of 42 animals receiving the above materials, 35 demonstrated response PS. Of these, 8 out of 10 receiving plasmodial fraction E_1 exhibited a PS response (Table 2).

None of the 99 mice receiving plasmodial fractions C_2 , C_3 , E_2 , E_3 , or any of the normal host cell preparations R, S, T, T_1 , T_2 , and T_3 demonstrated a protective response. Of the 99 animals, 86 died (response NS) and 13 eventually recovered after a severe infection (response NPS) (Table 2).

The above results confirm the previous finding that the artificial protection against malaria noted here is induced by a particular fraction of plasmodia (4, 7, 8) rather than by host cell contaminants. The protective fraction is contained in the partially purified plasmodial material contained in the Sephadex G-200 void volume eluates E_1 and C_1 (8).

Although various plasmodial preparations have been evaluated for protective properties (4, 7-9), the E_1 fraction prepared in our studies is the most highly purified material thus far shown to induce resistance to malaria. Moreover, in addition to its immunogenic properties, the E_1 fraction has

proved an excellent complement-fixing antigen. It is highly specific, sensitive in serological evaluations, and is free from serologically detectable amounts of host erythrocyte stromata (5, 10).

Successful demonstration of the protective properties of partially purified plasmodial fraction E_1 opens the way for definitive studies of relations between host and antigen in malaria, as well as final purification and characterization of potential malaria vaccine materials.

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12. We thank C. Gaines for assistance and Dr. N. Alger for the *P. berghei* NK65D strain. Supported by the U.S. Department of State Agency for International Development, contract AID/csd-1432.

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Marihuana and Temporal Disintegration

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Abstract. High oral doses of marihuana extract, calibrated for content of 1(-)- Δ^1 -tetrahydrocannabinol, significantly impaired the serial coordination of cognitive operations during a task that required sequential adjustments in reaching a goal. This disintegration of sequential thought is related to impaired immediate memory.

Clinical studies (1) of temporal distortions and disorganized speech in acute schizophrenia, as well as pilot studies with tetrahydrocannabinol (THC), led us to be interested in temporal disintegration. Temporal disinte-

gration means that the individual has difficulty in retaining, coordinating, and serially indexing those memories, perceptions, and expectations that are relevant to the goal he is pursuing. Our findings indicate that (i) high oral doses

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of THC induce temporal disintegration in normal subjects; (ii) the phenomenon stems partly from impaired immediate memory; and (iii) temporal disintegration is associated with disorganized speech and thinking.

Temporal disintegration was measured by a task, termed the "goal directed serial alternation" (GDSA), which required that the subject simultaneously hold in mind and coordinate information as well as mental operations relevant to pursuing a goal (2). After giving the subject a starting number between 106 and 114, we asked him to subtract 7, then add 1, 2, or 3, and repeat such alternate subtraction and addition until he reached an exact goal between 46 and 54 that we specified for each trial. In this way, we randomly varied the starting point and goal from trial to trial so that different cognitive adjustments were necessary for each test session. We asked the subject to recite his mental operations out loud and to work as rapidly and accurately as possible, without his using written props. The overall performance score for the GDSA gives equal weighting to the time taken in seconds to perform the task and to the number of mistakes made (3). Higher GDSA scores indicate greater temporal disintegration.

We employed two other cognitive tasks that are relevant to short- and long-term memory functions (4) necessary for performing the GDSA. The "regular serial subtraction of sevens" required that the subject begin at a specified number around 100 (± 4), which again was varied at random, and then subtract sevens serially until zero was passed. Each separate subtraction makes use of simple arithmetic operations filed in long-term memory. Like that for the GDSA, the overall performance score on this task gives equal weighting to the time taken in seconds and the number of mistakes made (5). The tests of short-term memory, the "digit spans forward and backward," were measures of the number of digits that the subject could accurately reproduce in the same or reverse order of presentation. The experimenter read a series of random digits at a steady rate of 1/sec. He then recorded as the subject's digit span, forward or backward, the largest number of digits that the subject could reproduce without error on two successive trials. For all

Table 1. Cognitive tasks and THC doses tested by analysis of variance (d.f. = 3, 21). Performance on GDSA is measured as the time (seconds) + C times (1 + number of mistakes), where C equals 39. Performance on regular serial subtraction of sevens is measured as the time (seconds) + C times (1 + number of mistakes), where C equals 27 seconds. Performance on the "digit spans forward and backward" is measured as the number of digits that the subject could accurately reproduce in the same or reverse order of presentation. Not significant, N.S.

Dose of THC (mg)	Performance in tasks (mean)			
	Goal-directed serial alternation	Regular serial sevens	Digit span forward	Digit span backward
Placebo	130.4	77.3	9.0	7.8
20	194.6	87.9	8.2	6.9
40	244.7	101.8	8.1	6.6
60	294.9	111.9	7.9	6.4
F	9.2	2.4	4.5	5.2
P	.001	N.S.	.05	.01

the upper limit of the subject's capacity for each testing session.

Tetrahydrocannabinol was extracted from marihuana supplied by the Bureau of Narcotics and Dangerous Drugs. Thin-layer and gas-liquid chromatography of these extracts showed predominantly $1(-)-\Delta^1$ -THC, with smaller amounts of cannabidiol and cannabinol. The oral doses used in this study, quantitatively calibrated according to the content of $1(-)-\Delta^1$ -THC, were 20, 40, and 60 mg of THC. The extract contained 20 mg of $1(-)-\Delta^1$ -THC per milliliter of 95 percent ethanol diluted in water to an acceptable degree. We also used a placebo, composed of an extract of marihuana from which virtually all of the cannabinoids had been removed. It retained the characteristic disagreeable taste of the active material. The 40- and 60-mg doses are probably considerably higher than those obtained from the usual custom of smoking marihuana in social settings. However, previous studies of equivalent oral doses of synthetic $1(-)-\Delta^1$ -THC (6) suggest that the induced psychotomimetic effects are clinically similar to those associated with smoking potent marihuana. Thus, one need not be concerned about the relevance of studying the effects of ingested rather than smoked marihuana. The oral route of administration, at least at present, offers a far more precise way of regulating dosage.

Using double-blind controls, we gave eight normal male graduate students the three oral doses of marihuana extract or placebo in randomized order on four different test days separated by at least 1 week. Doses were ingested after at least an 8-hour fast. Subjects were tested before drug ingestion (base line) at 1, 1½, 2½, and 5½ hours after

ingestion. The same psychiatrist tested the same subject in an isolated, somewhat austere room on each of the experimental days. Both psychiatrist and subject knew that THC was to be given, but they were unaware of the sequence of the various doses and placebo.

Increased doses of THC progressively impaired GDSA performance (Table 1). Also, there were significant differences between performances on the GDSA at different doses. The poorest GDSA performances took place 1½ hours after THC ingestion, but there was a significant interaction between dose and time of testing ($P < .025$), an indication that higher doses prolonged temporal disintegration as measured by the GDSA. For example, 5½ hours after the 60-mg dose, scores still differed 150 percent from base line.

By contrast, performance on the "regular serial subtraction of sevens" was not significantly impaired by THC (Table 1). Sustained attention and long-term memory operations, which are required by the task (7), appear not to be affected by THC. On the GDSA, moreover, with increasing doses of THC, there were no significant increases in mistakes of long-term memory operations as reflected in miscalculations (that is, errors in addition and subtraction).

Short-term memory, however, was impaired by THC. Both forward and backward digit spans were significantly decreased by all doses of THC (Table 1), although there were no significant differences between doses. Also, for all doses, digit spans returned to near base line at 3½ hours. Thus, in contrast to the progressive and more prolonged GDSA difficulties, impairment of the digit spans was not augmented by high-

Table 2. Mistakes on the GDSA are compared, by the Wilcoxon matched-pairs signed-ranks test (two-tailed), with respect to the condition under which they occurred (non-drug versus drug) and with respect to the point at which they occurred—that is, early (before subject reached the number 80 in the test) compared to late (after subject passed 80). Mistakes made during 48 non-drug trials (placebo and base line) are compared to those made during 48 drug trials (all doses of THC at 1½ and 3½ hours after ingestion). Not significant, N.S.

Trial	Serial immediate memory mistakes			Miscalculations		
	Early	Late	P	Early	Late	P
Non-drug	5	3	N.S.	16	18	N.S.
Drug	20	65	.01	26	23	N.S.
P	.05	.01		N.S.	N.S.	

er doses. This suggests that factors other than the span of short-term memory may be involved in temporal disintegration.

Analysis of types of mistakes made during performance of the GDSA showed that, with increasing doses of THC, there were progressively more errors in the serial or "working" functions of immediate memory ($P < .035$, Wilcoxon matched-pairs signed-ranks test). Serial immediate memory errors include loss of place, failure to alternate between subtraction and addition, and blocking (3). Compared to the short-term retention of a list of items, as measured by the digit spans, serial immediate memory requires the subject to keep track of inputs at the same time that he manipulates them. Difficulties in this process appear to be involved in temporal disintegration, because during GDSA performance THC induced significantly more serial immediate memory errors, as opposed to miscalculations, when subjects got nearer to their goals—that is, when they had to begin making adjustments to reach their goals exactly (Table 2). In switching back and forth between their most recent operation and the goal, in the attempt to temporally link the means to the end, the subjects frequently lost track of where they were in the serial process. To quote one subject, "I'd pick out a number now and then go ahead. . . . Coming back, I'd forget which number I just did or what I was supposed to do next."

Furthermore, with increasing doses of THC, there were progressively more errors in reaching the goal. Of particular relevance to temporal disintegration is the mistake of disregarding the goal,

ditions. Here, subjects kept going right past the goal until they later checked themselves when they realized they had not brought the goal, which they remembered accurately, into awareness at the right time.

This temporal incoordination of recent memories with intentions may account, in part, for the disorganization of speech patterns that occurs under marihuana intoxication (8). As one subject remarked, "I can't follow what I'm saying . . . can't stay on the same subject . . . I can't remember what I just said or what I want to say . . . because there are just so many thoughts that are broken in time, one chunk there and one chunk here." These difficulties are similar to the breakdown of goal-directed serial operations during performance of the GDSA. In this regard, the construction of meaningful speech requires that words and phrases be hierarchically ordered in a goal-directed fashion (9). If there is a deficiency in immediate memory, the components of speech become poorly interconnected over time, and the person is apt to lose his train of thought (10). Hence, "loose associations" emerge, since ideas are determined primarily by very recent or current stimuli rather than by a more extended temporal context of what has already been said and what is intended. Lack of goal-directedness and loose associations were common in the speech patterns of our subjects when they were under the influence of THC.

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2. Temporal disintegration was also measured by a subjective inventory that tapped the subjects' appraisal of how well they could plan ahead without confusing elements of the past, present, and future. Changes in this inventory correlated highly with changes in GDSA overall performance ($r = .719$, $P < .0001$). Both the inventory and the GDSA are rooted in the conceptual framework presented by G. A. Miller, E. H. Galanter, and K. H. Pribram [*Plans and the Structure of Behavior* (Holt, New York, 1960)] and by K. H. Pribram and F. T. Melges [in *Handbook of Clinical Neurology*, P. J. Vinken and G. W. Bruyn, Eds. (Wiley, New York, 1969)].
3. Overall performance on GDSA is measured as the time (seconds) $+ C$ ($1 +$ number of mistakes), with C equal to 39, which was the average number of seconds associated with errorless performance for all subjects on their base-line testing. Types of mistakes, which were scored and checked by two observers without knowledge of dose, are as follows. Forgetting instructions was the inability to repeat back out loud the required procedure before starting the task. Miscalculations were errors in arithmetic, involving the long-term memory operations of subtraction and addition. Serial immediate memory errors consisted of loss of place; no alternation between subtraction and addition; and blocking—that is, having to restart or skipping at least 20 numbers. Mistakes in reaching the goal consisted of forgetting the goal; disregarding the goal; and misadjustment to the goal, stemming from inadequate planning. Since the GDSA is a goal-directed task, failure to reach the goal exactly was weighted as three mistakes for the overall GDSA performance score.
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Metastable Oxygen: Origin of Atmospheric Absorption near 50 Kilometers

Krueger (1) has reported unexpectedly large atmospheric absorption (not due to ozone) near 3000 Å from observations made above an altitude of 30 km. He concludes that the column abundance of the new absorbing species above 50 km is about 5×10^{16} cm⁻², assuming a fully allowed, absorbing transition with a cross section

didates for the absorber he considers the metastable oxygen $O_2(b^1\Sigma_g^+)$, $O_2(a^1\Delta_g)$, and vibrationally excited O_2 near $v = 11$ in the ground state $O_2(X^3\Sigma_g^-)$.

There is strong evidence against all three candidates, which is based on rocket measurements of the dayglow. Although a theoretical estimate, quoted by Krueger, suggested that the abun-

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ADVERSE REACTIONS TO MARIHUANA*

Classification and Suggested Treatment

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Abstract Adverse acute reactions to marihuana are infrequent, but physicians will see more of them as use of the drug increases and reaches new areas of society. Several very distinct types of reactions occur. In persons without a history of mental disorder who have never taken hallucinogenic drugs, marihuana may cause simple depressive reactions, panic reactions (most common) and toxic psychoses. In persons who have previously

AS the recreational use of marihuana has become more and more common in the United States, physicians have begun to see adverse reactions to the drug. Because reliable information about the acute effects of marihuana has been as scarce within the medical profession as without, many of these reactions have been misinterpreted and incorrectly treated. For example, simple panic states, which doubtless would be properly diagnosed in other circumstances, are often called "toxic psychoses" when doctors elicit immediate histories of marihuana use.

Over the past two years, in conjunction with experimental studies of marihuana in Boston^{1,2} and during hospital practice in San Francisco, I have interviewed hundreds of users and have had an opportunity to see and treat many adverse reactions to marihuana. It has become clear to me that these are by no means all of a like nature but rather fall into distinct categories that require different thera-

taken hallucinogens, marihuana may also trigger recurrences of hallucinogenic effects and may occasionally precipitate delayed psychotic reactions. Finally, in ambulatory schizophrenics, marihuana can cause atypical reactions, frequently marked by derealization. Most of these reactions are self-limited and benign but can be worsened by improper medical management. A few require psychiatric and psychopharmacologic intervention.

peutic approaches. A scheme of classification, illustrated with case examples and accompanied by suggestions for management, is offered here.

ADVERSE ACUTE REACTIONS TO MARIHUANA

In Persons without a History of Mental Disorder Who Have Never Taken Hallucinogenic Drugs†

Miscellaneous, mild ill-effects of marihuana (such as nausea, headache and transient paranoia) are familiar to most users, but serious adverse reactions to the drug are uncommon in the "normal" population. Many persons who smoke marihuana experience no subjective effects at all,¹ but most of those who do get high find the effects pleasurable. I have encountered three types of exceptions:

*"Hallucinogenic drugs" include LSD, mescaline, psilocybin, DMT (dimethyltryptamine) and their derivatives, all of which have the structures of indoles or substituted amphetamines, stimulate the sympathetic nervous system and cause visual hallucinations at subtoxic dose levels. Marihuana has no relation to these drugs — chemical, pharmacologic or clinical — even though it keeps company with them in drug-using subcultures. No derivative of cannabis causes true hallucinations except as a manifestation of toxic overdose.

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Simple depressive reactions. In neophyte users (rarely in regular users) marihuana may precipitate acute depressions that sometimes come to the attention of psychiatrists. It is not clear that marihuana has any specific pharmacologic effect on mood²; in fact, the traditional euphoria of a high may well come from set and setting rather than drug. Marihuana depressions I have seen have occurred mainly in obsessive-compulsive persons who were ambivalent about trying the drug or who invested the decision to experience marihuana with great emotional meaning. In interviewing these patients, I have thought that they used the marihuana as an excuse for letting themselves be depressed, not that their depressions were psychopharmacologic. Of the simple depressive reactions to marihuana that I have seen (20 cases), all have ended spontaneously, and all have resembled transient neurotic depressions unrelated to marihuana.

Panic reactions. The majority (over 75 per cent of my cases) of all adverse responses to marihuana are panic reactions in which people interpret the physical or psychologic effects of the drug to mean that they are dying or losing their minds. Panic states may become so severe as to be incapacitating and may simulate acute psychosis, especially in the setting of a hospital emergency ward, where the patient may feel overwhelmed, helpless and unable to communicate his distress. Because these reactions arise from combinations of set and setting, their frequency varies greatly from locale to locale. In a community where marihuana has been accepted as a recreational intoxicant, they may be extremely rare (for example, 1 per cent of all responses to the drug). On the other hand, at a rural Southern college, where experimentation with the drug may represent a much greater degree of social deviance, 25 per cent of persons trying it for the first time may become panicked.

In my opinion, all adverse marihuana reactions should be considered panic reactions until proved otherwise. This diagnosis not only is by far the most likely on a statistical basis but also represents the only condition whose outcome is crucially dependent on the initial response of the physician. Panic states can always be terminated by simple reassurance. If the doctor approaches the patient as a psychiatric emergency (by administering tranquilizers or urging hospitalization), he will often prolong the panic by inadvertently confirming the patient's fears of a mental breakdown. Diagnosis of the panic reaction to marihuana is easy if the following points are kept in mind: most patients are novice users of marihuana — frequently older persons or persons who were ambivalent about trying the drug in the first place; patients are *not* psychotic, but panicked — their reality testing is intact; patients are always able to relate their dis-

tress to the consumption of the drug; the main disturbance is one of affect (patients may be anxious, depressed, tearful, withdrawn or agitated, but they are not disoriented and do not hallucinate); and there is a marked response to gentle but authoritative reassurance that nothing is seriously wrong.

CASE 1. R.T., a 24-year-old medical student, arrived in San Francisco from New York to take a summer externship in internal medicine at a private teaching hospital. He had used marihuana infrequently and had "never really gotten high on it." On his 1st night in San Francisco he was depressed about troubles with his family, girl friend and schoolwork, but he accepted an invitation to a party given by several residents at the hospital. At the party he smoked "a lot of marihuana — stronger than I've ever had." He began to think that he was unable to understand what was being said to him and that he could not talk sensibly to others. He then became convinced that he was having "an acute psychotic reaction" and asked to be taken back to his room in the hospital. A resident gave him a 25-mg tablet of chlorpromazine hydrochloride (Thorazine), and he went to sleep. On the next morning he awoke depressed. By mid-morning he was in the midst of an acute anxiety attack and went for help to another resident, who gave him 2 capsules of chlordiazepoxide hydrochloride (Librium). At that time he was pale, sweating, agitated and withdrawn. He asked all who approached him whether they thought he was losing his mind, and said repeatedly that he wanted to go back to New York. Over the next 12 hours he was given more chlordiazepoxide and chlorpromazine, as well as amateur psychotherapy by several medical residents, but showed no improvement. Finally, a physician recognized the nature of his reaction and dealt with it successfully by reassuring him that he had experienced an unusually strong marihuana high, now dissipated, that he was not becoming psychotic, and that he did not need any more tranquilizing medication. The patient gratefully accepted this reassurance and improved so rapidly that he was able to assume his externship duties on the following day. Afterward, he agreed that he had been "letting [himself] get frightened" but said he would not smoke marihuana again "for some time." He was advised to consult a psychiatrist about his underlying depression, which appeared to be situational.

CASE 2.* L.H., a 37-year-old New York housewife, was persuaded by her 15-year-old daughter to "turn on" by eating candy made with hashish. She had never tried cannabis before and agreed to do so out of "curiosity" although she was very apprehensive. The daughter ate 3 times as much candy as the patient and became "pleasantly high" for about 6 hours. The patient, 1 hour after ingesting the candy, felt her heart racing and thought she was going to have a heart attack. She became panicky and lay down without telling her daughter what was wrong. Shortly afterward she felt "flushed and dizzy" and became convinced that she was poisoned. Finally, she got the daughter to call a family physician, who persuaded the patient to take a taxicab to a nearby emergency ward. When the physician arrived at the hospital he found her in a state of nervous collapse with a regular heart rate of 140.[†] He ordered an intramuscular injection of chlorpromazine and had her admitted to a psychiatric bed. She remained agitated and depressed for 4 days and was discharged on the 5th day with no aftereffects. The

*Smith³ has reported a similar case from the West Coast.

[†]Tachycardia, a true pharmacologic effect of marihuana,¹ is often the basis of cardiac anxiety in panic states, especially in older persons.

daughter, who had taken 3 times the dose of hashish, had a "good time" that lasted about 6 hours.

The physician should treat panic reactions by reassuring the patient that the drug is not causing him any serious or permanent effects and will wear off in several hours. Medication and hospitalization are contraindicated except in cases of extreme agitation, when mild sedation may be desirable (I would prefer phenobarbital to a phenothiazine, minor tranquilizer or short-acting barbiturate). Psychiatric referral is indicated only if underlying psychopathology becomes manifest during the panic state.

Toxic psychoses. Toxic psychoses (or acute brain syndromes) are temporary malfunctions of the cerebral cortex due to the presence of toxins in the body; they disappear when the toxins disappear. The reaction is a nonspecific one that can occur to overdoses of many intoxicants and medications, including marihuana. However, although I have seen a number of toxic psychoses resulting from orally ingested cannabis (10 cases), I have never seen one that followed smoked marihuana. In fact, when one smokes very potent marihuana continuously, after a certain point one does not become any higher — only more sedated. This observation is one reason for thinking that hemp drugs may have qualitatively different effects according to the route of administration (possibly because certain toxic constituents of cannabis resin that get into the body when the drug is eaten are destroyed by the heat of smoking).⁴ The clinical manifestations of a toxic psychosis are quite constant and should be unmistakable; they closely resemble the delirium of high fever. Patients are disoriented, confused and frequently prostrate. Hallucinations, both auditory and visual, are common.

CASE 3. T.W., a 24-year-old law student who smoked marihuana daily and "never had any difficulty with it," read that Baudelaire had obtained hallucinatory experiences by drinking suspensions of powdered hashish in coffee. Accordingly, he obtained a "1/2-inch cube" of hashish, powdered it, suspended it in coffee, and drank it on an empty stomach in the early evening. He described his subsequent experience as follows: "I didn't feel anything for about 40 minutes. Then I gradually started feeling high, and the feeling intensified over the next 20 minutes. About 1 hour after I had finished the coffee, I suddenly felt higher than I ever had after smoking hashish, and I also began to feel sick. Then everything became very confusing. I couldn't make sense of what people were saying or what was happening. I don't remember very well what happened next. I think I went to bed and just lay in misery for about 6 hours. The only thing I can compare it to is what I remember it was like to have measles as a child, when I had a temperature of 105°F. I know I saw crawling patterns on the walls and heard very unpleasant voices calling me. I also couldn't recognize or talk to people who came into the room to find out how I was. I fell into a fitful sleep sometime after midnight and had horrible nightmares. In the morning I felt exhausted and washed out, but the worst of it was over. I ached all over and had a headache and hangover for a day and a half."

Toxic marihuana psychoses are self-limited and not dangerous as long as the patient does not sustain injury as a result of his disorientation. However serious such a reaction may appear, the physician should remember that the world literature on cannabis does not report a single fatal case due to the drug. No medication is indicated in a toxic psychosis except in the postpsychotic phase, when symptomatic relief of physical aftereffects may be offered. Talbott and Teague⁵ have recently reported several cases of "toxic psychosis" associated with marihuana use among soldiers in Vietnam. I would not include them in the category of "toxic psychosis" as I have defined it. I do agree with the authors that many of the peculiar features of their cases are related to the very special conditions of set and setting that obtain in Vietnam.

In Persons without a History of Mental Disorder Who Have Previously Taken Hallucinogenic Drugs

In addition to the three reactions listed above, persons who have previously taken hallucinogens may experience two other forms of adverse reaction to marihuana.

Recurrence of hallucinogenic symptomatology ("flashbacks"). Marihuana smokers who try hallucinogens occasionally find that marihuana highs change for them after their hallucinogen experiences. A common form of this phenomenon is the repeat experience of a simple hallucination. For example, a person who saw the petals of flowers move and breathe when he was under the influence of mescaline might see the same thing on looking at flowers a few days later while high on marihuana. Some people interpret these recurrent symptoms as pleasant — even desired — experiences. Others find them unwelcome and disturbing. Hallucinogen flashbacks certainly occur independent of marihuana, but I have seen eight patients who experienced them only when taking cannabis.

CASE 4. M.N., a 49-year-old psychiatrist, had smoked marihuana about once a week for 3 years; he used it as a recreational intoxicant and enjoyed its "relaxant effects." Then he tried LSD out of curiosity and found the experience "unpleasant." Subsequently, he discovered that he could no longer enjoy marihuana because whenever he smoked it he re-experienced the LSD effects. He now does not smoke marihuana at all and has not tried any other psychoactive drugs.

Flashbacks are benign in most patients and tend to fade out as the hallucinogenic experience recedes in time. If the patient abstains from marihuana, there should be no recurrence.

Precipitation of delayed psychotic reactions to hallucinogenic drugs. A small percentage (the exact number is unknown) of persons who take hallucinogens subsequently suffer delayed psychotic reactions that may not appear until several

months after the last use of the drug. These reactions are sometimes unrelated to any previous history or indication of mental illness, and they are often resistant to treatment. In some cases they have clearly been triggered by acute marihuana intoxication; there is no way of knowing whether they would have happened anyway, of course.

CASE 5. G.M., a 24-year-old writer with no psychiatric history, had smoked marihuana frequently for 1 year. Then she began experimenting with hallucinogens with her boyfriend. She took LSD 3 times and mescaline once. Three months after her last hallucinogenic experience (she continued to smoke marihuana), she broke off her relation with her boyfriend and returned to her parents' home in New York. Shortly after her arrival there, on a weekend night, she got very high on marihuana by herself and to her surprise began to re-experience hallucinogenic symptoms. Over the next 48 hours she suffered a severe psychotic decompensation and had to be hospitalized involuntarily. A diagnosis of acute paranoid schizophrenia was made, and high doses of phenothiazines were begun. After 4 weeks she was able to be discharged to outpatient therapy. One year later she suffered a 2d psychotic break requiring hospitalization for 7 months. She is now attending graduate school and is still receiving phenothiazines and psychotherapy. She has not used marihuana or other psychoactive intoxicants since the onset of her illness.

In Persons with a History of Psychosis

Most people who become high on marihuana find the effects pleasant. A surprisingly high percentage of those who find the effects unpleasant turn out to be ambulatory patients with schizophrenia. In fact, patients with a low threshold for psychosis often shun marihuana after an initial encounter.

CASE 6. R.S., a 26-year-old writer who had been given the diagnosis of ambulatory schizophrenia but had never been hospitalized, smoked marihuana for the 1st time at a party in New York but did not consume enough to become high. A few months later she tried it again with a friend and did become high. After a few minutes of euphoria, she had the experience that things became "unreal and weird," and she grew anxious. Her anxiety increased, and she became very withdrawn. The "weird" sensations persisted for 48 hours and then subsided. Afterward, she said that she "would never touch pot again."

My experience with these reactions is limited (five cases), but it appears to me that in borderline personalities, the effects of marihuana on secondary perception⁴ may constitute a stress that pushes pa-

tients in the direction of derealization, an experience generally perceived as frightening. Psychotherapy and antipsychotic medication appear to bolster the patient's defenses against this reaction and should be used as the psychiatrist deems appropriate.

The occurrence of these atypical reactions to marihuana in persons with low thresholds for psychosis suggests that the drug might also be capable of precipitating true psychotic breaks in these patients. I have never encountered such a reaction, myself, but Smith and Mehl⁶ have reported them. They comment: "...[In such cases] the psychosis is characteristic of the personality structure of the user, not of the drug. The intoxication merely triggers the psychosis, as is seen with a variety of other drugs including alcohol, amphetamine, and LSD."

DISCUSSION

Adverse acute reactions to marihuana occur but are rare on a statistical basis except in areas where anxiety about the drug is high. Panic reactions, which seem more nonpharmacologic than pharmacologic, are most common, and correct diagnosis is essential if the physician wishes to end them instead of prolonging or intensifying them. Marihuana does not seem to trigger true psychotic reactions except in persons with a history of psychosis or hallucinogenic-drug experimentation. Most adverse responses to the drug are self-limited and respond to a common-sense approach, combined with gentle but authoritative reassurance that nothing is seriously wrong. In the rare cases of toxic psychoses, delayed psychotic reactions to hallucinogens and atypical reactions in ambulatory schizophrenia, time and other measures will also be needed.

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A Comparison of Marijuana Users and Non-users

by

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Interviews with sixty-two Americans in their twenties, mostly students, demonstrate that those who smoked marijuana moderately differed little in personality from those who did not indulge, but that heavy smokers of marijuana were rather less conventional. The smokers tended to drink little alcohol.

We have already reported the results^{1,2} of pilot human experiments with marijuana*. Those articles dealt principally with the subjects' responses to the drug itself and did not include many other observations made in the course of acquiring volunteer subjects, providing for their safety and assessing the long-range effects on them of their participation in the research. Interesting social and psychological similarities and differences were revealed among three groups of subjects: marijuana naïve persons (N), persons not naïve to marijuana (NN) and chronic marijuana users (C). We discuss these results here.

Obtaining Volunteers

In the experiment two groups of subjects were tested. The first consisted of nine male volunteers, at least 21 years old, who smoked tobacco cigarettes regularly but had never tried marijuana. The second group consisted of eight regular marijuana smokers (average frequency of use: once a day for several years), who were recruited by passing word among the staff of an underground newspaper that heavy marijuana users were needed for experiments with the drug. Nine men volunteered and were given appointments for screening interviews. These nine make up the C group in this discussion.

The nine naïve subjects were selected from a pool of interviewees who were recruited by advertisements in college newspapers in the Boston area asking for volunteers for "psychological experiments". (There was no indication that the experiments concerned marijuana or other drugs.) All who responded to the advertisements were asked whether he drank or smoked tobacco. The non-smokers (of tobacco) were eliminated. We were unable to find enough marijuana naïve smokers who smoked enough to inhale deeply and easily, and we resorted to more active methods of recruiting in areas where we thought marijuana use might be low, but we had no more success.

Eventually sixty-two prospective subjects, including the nine known chronic users of marijuana, were interviewed in depth by a psychoanalyst. Fifty-three had responded to our advertisements in college newspapers. Twenty-eight of these had used marijuana at least once and were therefore eliminated from the experiment; they make up our NN group. The other twenty-five were marijuana naïve and make up the N group. Our sample is not representative of the general college population in Boston, but it is probably a fair sample of those in the college population of Massachusetts willing to answer an advertisement for an unspecified psychological experiment.

* These experiments were carried out, with the help of Miss Judith Nelson, while we were guests at the laboratory of Dr Conan Kornetsky and Dr Peter Knapp of Boston University Medical School.

Interviews

All subjects were interviewed in the same way, although once a candidate was identified as a non-smoker the interview tended to be shorter. The interviewer began by obtaining the subject's permission to ask somewhat personal questions, reassuring him that only group findings would be reported.

The interviewer asked about the general educational, geographical and social background of the subject and his family. The subject's emotional relationships with family and friends were discussed, along with medical history, including any psychiatric contact, actual or considered. There were general questions about use of cigarettes, alcohol and other drugs during a discussion of social habits, but detailed questions were held until near the end of the interview. The interviewer tried to determine the subject's economic, political and aesthetic attitudes and values, pausing for more specific questions in any area that interested the subject, caused him to become more reticent or seemed important in other ways for the further delineation of character structure.

The interviewer then questioned the subject in depth about drugs. If he admitted having tried any drug, he was asked exactly what he had taken, who had given it to him, whether he had given it to anyone else, what it had felt like and what he saw as the long-term effects of the drug use on his personality, attitudes and behaviour. If he had not taken any drug, he was asked whether he had had the opportunity to do so. He was also asked to discuss any knowledge of drug use he had obtained from friends or from the mass media, and to give his own overall attitudes toward drugs. Until the end of the interview, none of the subjects guessed that drug use was a principal focus. In the opinion of the interviewer, all the material we presented was offered freely and seemed reliable.

Information Elicited

The subjects ranged in age from 21 to 27, clustering around 23 to 24. Although we assigned them to the three groups—N, NN and C—the actual drug use of some of the NN group approached that of the Cs. All but two in each of the three groups were students in eight different institutions of higher learning in the Boston area. Of the rest, all but one (an N, diagnosed as a chronic schizophrenic, who will not be included in the tables to follow) were employed.

Drug histories of the different groups are quickly summarized. Two N subjects took occasional amphetamines without prescription during examination pressures; one took cortisone for medical reasons and one was pathologically sensitive to a variety of drugs. (The latter two were disqualified from the experiments.) Of the NN subjects, one had tried marijuana once, seven had

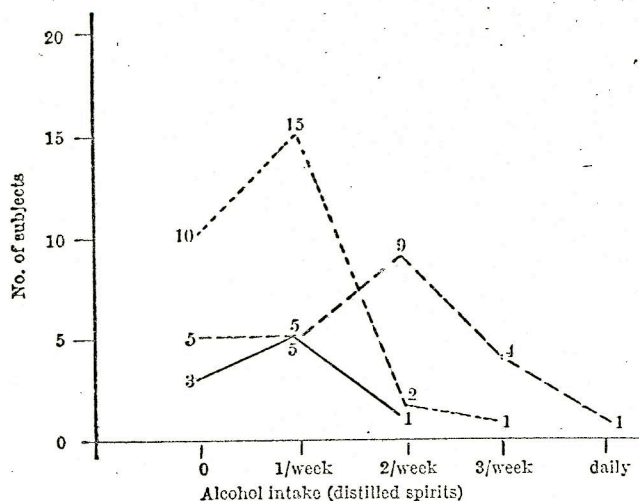


Fig. 1. Subjects' consumption of alcohol. ---, NN (28); ----, N (24); —, C (9).

taken it "a few times"; the rest used it regularly—weekly or even daily. Fifteen NN subjects had tried hashish, and four had used LSD (two once, one twice, and one six times). All the C group had tried hashish; four of them had taken LSD. One subject had taken LSD twice, mescaline twice, and methedrine, cocaine and heroin once each. Another had taken LSD three times and heroin once. Both of these had been overseas in unusual circumstances when they had tried heroin several years before the interview, and neither had tried it again. All regular users in the NN group and all the C group said they had ready access to a variety of psychoactive drugs.

Questions about alcohol intake produced interesting information. For the NN subjects it seems that, when marijuana use became regular, the use of alcohol, especially distilled spirits, declined proportionately or even more steeply (Fig. 1). In the C group, with one exception, no subjects drank alcohol except as part of the marijuana smoking ritual when they sipped cold beer or wine to relieve dryness of the mouth. In fact, three of the nine C subjects virtually never drank alcohol, and one other reported a definite distaste for drink even before he started using marijuana.

Questions about parental drug use elicited direct responses from eight Ns, eighteen NNs and five Cs. Three said that both parents were constantly on medication: tranquillizers, sedatives, insulin, antihistamines and digitalis were mentioned more than once. What impressed the interviewer were the promptness of reply and the extent of knowledge about parental medication, even by subjects who had been home infrequently in recent years.

In terms of socio-economic distribution of families, the N and NN groups differed hardly at all; nor was there any difference between the two in closeness of relationship with family, as rated by the subjects themselves on an arbitrary scale of 1 to 5. By contrast, the C group had more affluent backgrounds (Figs. 2 and 3), but this fact is probably a recruitment artefact: nineteen of the N subjects and eighteen of the NNs gave a desire to earn money as the reason for volunteering for the experiment, while only one of the C group gave that reason. The C subjects also had more prominent histories of family disturbance.

Ns and NNs corresponded almost exactly on courting behaviour and political attitudes. Most saw a girl about once or twice a week; three in each group were married. Most mentioned names like Rockefeller, R. Kennedy and McCarthy as presidential choices (interviews were held in the spring of 1968), opposed the war in Vietnam and

sympathized with student demonstrators (Fig. 4). The chronic users differed here. Four were married (one of these already divorced), and two more had been living with the same girls for nearly two years. Seven of the nine described themselves as radical or becoming radical and refused to choose a desired candidate for president from existing politicians (Fig. 5).

Personality Structures

At the end of the interview, the interviewer tried to place the subject on a rough gradient of personality traits ranging from extreme compulsiveness to extreme hysteria. The entire gradient is considered to fall within the limits of "normal" character structures.

The profile of a classic compulsive personality includes a desire for control over his life situation and, particularly, over his emotions. The compulsive individual always tries to maintain an emotional distance from other people, and his attempts are quite noticeable in a psychiatric interview. He also tends to use precise language (even if the ideas are highly generalized) to avoid the underlying indecision and ambivalence that create his need for control. These characteristics reduce his susceptibility to suggestion and his awareness of his inner life but help him organize successfully his outer life, relationships and work.

At the other end of the spectrum, the hysterical personality has ready access to his emotions and tends to use imagery rather than facts to express himself. As a result his relationships with others are more direct and he has a greater immediate awareness of his emotional responses in life. But he obtains this contact with his inner self at the expense of organization, continuity in relationships and thought, and precision of expression. He is also more susceptible to suggestion than the compulsive person.

Most people are mixtures of these two basic personality types. We tried to place our subjects on this continuum because we predicted that, in experimental conditions, hysterical personalities would be more likely to experience the subjective effects of marijuana. In our sample the N group showed a general tendency towards compulsiveness; the NN group tended towards more hysterical traits, and regular users (at least once a week) within the NN group clearly fell towards that end of the scale. Most subjects in both groups fell within the limits of the scale (that is, within the spectrum of normal personalities). By contrast, five of the nine C subjects fell off the scale and one more was only questionably within it. We shall call these personality distortions aberrations,

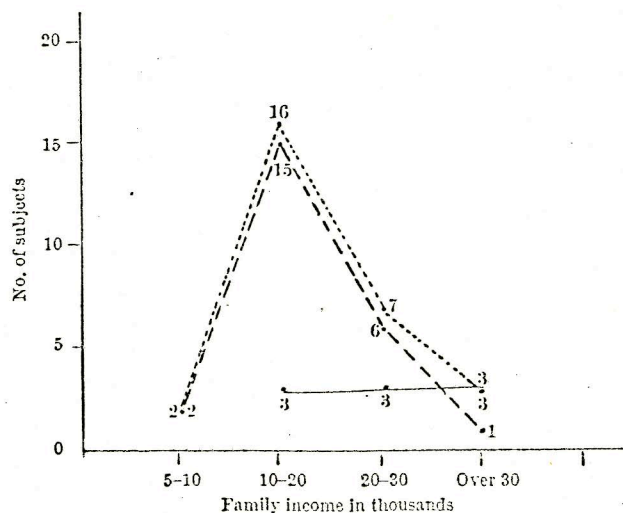


Fig. 2. Family income of subjects. ---, NN (28); ----, N (24); —, C (9).

although four of the six seemed well stabilized in their chosen environments.

Experiments and Beyond

Ultimately nine subjects were selected from the N group and eight from the C group to participate in the experiment. All the N subjects were given high and low doses of marijuana and placebos in double-blind conditions. Our prediction about personality type and subjective response seemed to be correct at each end of the scale. Subject 4 (J. G.), who had been rated the most compulsive and said he wanted to prove that marijuana did nothing, called his high dose a placebo, while subject 3 (T. P.), who had been rated the most hysterical and said he had many friends who like to use marijuana, was the only N to experience a subjective high.

All nine N subjects who participated in the experiment were interviewed six months after the completion of testing to see how their participation had affected them. These interviews were briefer than the initial ones and had the slight disadvantage of taking place a few days after the American presidential election. Because the subjects had been asked initially about their political attitudes, they thought it appropriate to discuss their positions at some length. This was in fact the only dimension that showed a significant change. Two subjects reported shifts to more conservative positions, while four had become more radical. All were continuing on their career tracks, with no change in family relationships or use of alcohol; one was now engaged.

They reported no significant changes in their attitudes toward marijuana. One had been at a party where a water pipe of marijuana was passed around; he had taken a few puffs with no effect. Another's friends, knowing of his participation in the experiment, had given him some of the drug as a birthday present. He said it was "not enough" for him to get high on, although a friend who smoked it with him and was a heavy user did get high. Another subject expressed a typical reaction when he said that he now has "no disinclination to try it again" but "no particular desire to seek it out". All nine subjects approved of the experiment and felt that more should be done to obtain knowledge about marijuana so that "kids won't get messed up" and the "law can be reviewed".

Who is Different?

We noted in the previous section that there were no significant differences between our N and NN groups on a whole series of basic psychological dimensions; family relationships, social class, educational achievement,

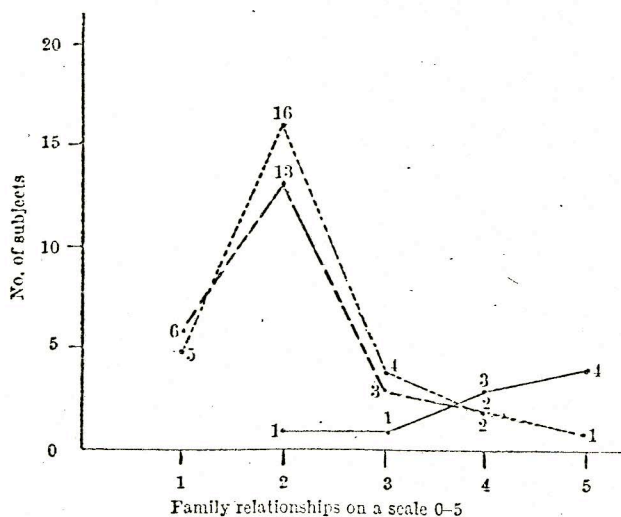


Fig. 3. Subjects' closeness to families., NN (28); ----, N (24); —, C (9).

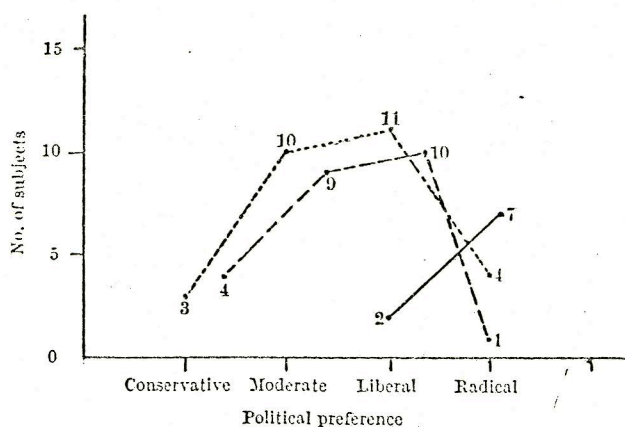


Fig. 4. Subjects' political attitudes., NN (28); ----, N (24); —, C (9).

financial status, sexual behaviour, political position and personality structure. Because the two groups were recruited in the same way, the lack of difference requires close attention. It suggests that the use of marijuana in the present student population may not signify any other differentiation. If this suggestion is proved, it would probably mean that marijuana use is now so extensive and so accepted within this particular age group that it cuts across all other boundaries.

Our failure to find greater evidence of overt neurosis in the NN group does not support the contention that marijuana use *per se* represents a neurotic outlet. Neither have we any evidence that marijuana users who began after 1966 form a well-delineated campus subculture with common backgrounds or characteristics (permissive parents, hippies, radicals and so on). We found this lack of uniqueness of the NN group remarkable and would not have predicted it in advance. Even though the NNs were slightly more susceptible to suggestion and more inclined to have a hysterical personality this is of borderline clinical significance and requires confirmation.

The C group, however, deserves special attention because it is easily differentiable from the other two. First, they regarded their drug use as the most significant single factor in determining their pattern of life.

Their constancy of attachment to female partners is not only out of line with the rest of our sample but significant compared with their age group in the general population or with a selected group matched for family background and educational achievement. This finding stands out because Vaillant's study of heroin addicts³ implied that 70 per cent maintained relatively stable marriages of common law arrangements: a remarkable figure considering the generally erratic nature of their lives, and one that contrasts sharply with those for other deviant groups (22 per cent for criminal delinquents). Vaillant uses the closeness to female partners in his argument that the heroin users he studied strove for closeness to a maternal figure and were unusually dependent.

Our C group has continued in school or chosen occupation, while Vaillant's group did not. But, as Fig. 5 shows, we did consider a significant portion of the Cs to be off our scale of usual personality structure. Supporting evidence for this rating was the extreme anxiousness and vague paranoia recorded during the interviews and persisting into the experiments. For example, the Cs had strong reactions against a blood sampling procedure. All of the Ns allowed blood to be drawn without incident, but three Cs complained of faintness, and two others wanted repeated reassurances that they would not be harmed. All nine commented repeatedly on that aspect of the experiment and gave strong indications that they did not want any tampering with their bodies.

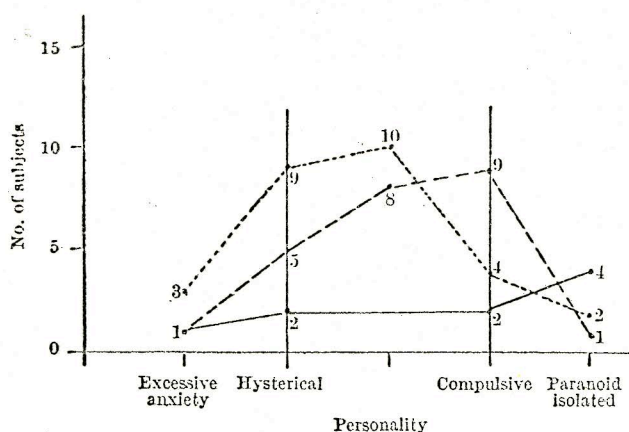


Fig. 5. Classification of subjects' personalities. NN (28); ---- N (24); — C (9).

In appearance the C group split about fifty-fifty with five recognizably hippy (long-haired and costumed) and four "clean-cut".

Two or three interviewees in both N and NN groups had unusual clothes, but none was as distinctive as the hippy members of the C group. There were signs of overt intellectual deterioration in the C interviewees, although several subjects talked with an unusual use of imagery and a general circumstantiality. Finally, their attitudes were quite negative toward society, which they saw as blindly conformist.

Hypotheses

We tried to explain these personality differences between the C and other groups by way of three hypotheses. (a) The C group was composed of persons who were more generally neurotic before they started using marijuana, and it was their need to express some personality distortion (excessive anxiety, paranoid tendency or excessive dependency) that pushed them into being chronic users of an illegal drug. (b) the Cs were "weaker", more suggestible persons who had succumbed to heavy marijuana use, and the drug itself caused the distortions now observed. (c) Choice of marijuana as a means of self-expression marks one as a deviant in the eyes of society and leads to fear of the police and other agents of the prevailing social order. Impact of these experiences on the C group produced the personality changes recorded in the interviews.

None of these hypotheses is satisfactory by itself. It is impossible to test the first without a prospective study. In retrospect, the Cs did not consider themselves unusually disturbed before marijuana use. They also did not see themselves as particularly susceptible to suggestion and rejected the idea that their involvement with marijuana had been unwitting. Many said their initial experience with the drug had been accidental or impulsive, but they considered the decision to use it regularly a rational one and under psychological control. Neither did they see themselves as "addictive personalities" who were hooked on intoxicants any more than most members of society. In fact, they tended to see themselves as freer and less interdependent than the rest of society.

Yet they did not reject the contention that their personalities had changed as a result of their use of marijuana. What the interviewer saw as greater circumstantiality, they saw as greater interest in abstraction or a use of the mind at a higher capacity. They evinced many doubts about the validity of Western thought, which they related to a greater interest in philosophy and—predictably—Eastern schools of thought.

By implication, the Cs themselves preferred the third hypothesis and saw it as a factor in their early decisions to marry. They were uniformly bitter about society's

attitude toward marijuana use and said this feeling affected their lives. Many reported that being defined as a deviant and law-breaker for something they could not accept as criminal had driven them into increasingly negative attitudes toward the larger society. Three subjects were especially articulate in tracing the shift of their values that led them to seek out individuals and groups who shared their positions and who used marijuana as frequently.

This argument, however, does not explain why the NN group had not reacted this way and had not allowed their drug use to become as dominant in their lives. A possible factor is that, although 60 per cent of the NN subjects were regular users, all began use after 1966 while all the Cs began use before 1965. The social atmosphere at the time the NNs began to use marijuana accepted the use more thoroughly, contemporaries were less likely to differentiate people as special (rebels or heroes) simply because of the drug use. Further, the NNs—even those whose use of marijuana approached that of the Cs—did not think of themselves primarily as members of a drug subculture.

Other Drugs and Alcohol

A negative finding that deserves some attention (and was a surprise to us) was the low frequency of use of drugs other than cannabis* in the NN and C groups. At first glance, the fact that almost 50 per cent of Cs had tried LSD and 20 per cent heroin may not seem low. But when one considers the ready availability of drugs to all members of this group, one must look further. In fact, if a single experiment with a drug ("one taste")⁴ is disregarded, then only 20 per cent have used any drug other than cannabis. And in those two cases (LSD and mescaline twice, and LSD three times) the use of these drugs was seen as a careful intellectual or philosophical exercise and was repeated ostensibly only for that purpose. In no case is there any evidence for any form of craving for further drug experience, although four Cs stated that at some future time they would like to try LSD (two again and two for the first time).

The figures for the NN group are even more remarkable. Of twenty quite regular cannabis users, only one (LSD six times) had used any other drug frequently. This finding bears on the question whether use of marijuana leads to the use of other drugs. With the exception of one NN subject who said he needed LSD "to further the enlightenment begun by marijuana", none of the subjects was moved by his cannabis experiences to the regular use of other drugs. We found no dissatisfaction with cannabis use that called for other drugs, and no subject expressed any fears of dependency on marijuana.

Lack of political activism among NNs is worth mentioning because it contrasts with findings of other interviews^{5,6} which show a high frequency of marijuana use among activists. Generally speaking, these writers suggest that the activism had been equated with rebelliousness, and this was not one of our findings. Greater use of drugs among NN parents, however, supports the possibility that illicit drug use can represent a rebellion/submission reaction to parents. In the US a young man can imitate and thus establish closeness with his elders by experimenting with drugs, but by taking the drug marijuana he can at the same time declare his independence and rebellion. There is some evidence for this possibility in our interviews, as exemplified by these statements: "My father would die if I told him I got the same tranquillizing effects from pot that he gets from his pills". And: "The first time I got high, I was in Cincinnati [parents' home], and I remember thinking that maybe Mom gets a kick out of all that junk she takes [antihistamines]"⁷.

* In differentiating between hashish and marijuana, the subjects confused power with potency—a common error. Hashish, as found in the US, is sometimes (by no means always) more potent than potent marijuana, but its effects are qualitatively the same when an equivalent dosage is taken.

Finally, it seems that alcohol intake decreases as marijuana use becomes regular. Because only one of the NN and none of the C subjects regarded themselves as heavy drinkers before using cannabis, it is not possible to infer that the same effect would be seen with regular drinkers of alcohol. But, in the case of the moderate use of alcohol associated with late adolescence and the early twenties, marijuana smoking seems to be a functional equivalent, not simply a further drug habit (contrast alcohol and nicotine, according to J. F. E. Shick, D. E. Smith and F. H. Meyers). The fact that many Cs were antipathetic to alcohol even before their initial

exposure to marijuana requires further study. We found that the surest indication of marijuana naivety is being a non-smoker. Possibly, a history of initial and persistent dislike of alcoholic effect will turn out to be correlated with subsequent chronic marijuana use.

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A Certain Symmetry: Histocompatibility Antigens compared with Immunocyte Receptors

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Recent work on cancer immunity suggests that the character and diversity of cell membrane antigens may be controlled by processes similar to those concerned with the origin of specific patterns in the immune system.

IN recent years immunologists have had a special interest in trying to bring immunological theory into a progressively closer relation to general biology. Pauling's concept¹ of antibody structure and production was invoked, but it became increasingly clear that this could not give expression to immunological phenomena in terms either of molecular biology or of its evolutionary significance. Since 1967 the clonal selection theory² has been acceptable in principle to all immunologists^{3,4} in so far as it involves: (1) The generation of a diversity of immune patterns (physically expressed in the amino-acid sequences of the "variable" segments in the light and heavy chains of immunoglobulins) by genetic processes having both germinal and somatic cell manifestations. (2) The differentiation of stem cells to immunocytes (morphologically cells of the lymphocyte series) carrying receptors capable of specific reactivity with appropriate antigenic determinants. (3) Phenotypic restriction by which each immunocyte clone carries only one specificity with regard either to the receptor or to the antibody it produces. If antibody is produced, it is of only one heavy chain type. (4) Selection by antigen of immunocytes and their stimulation to proliferate as (plasma cell) antibody-producing clones or as memory cells or immunocytes concerned with delayed hypersensitivity. Each of these four points was explicitly stated in 1957⁵; at present none is controversial. It has been striking to note how many experimental approaches with modern techniques have recently been applied to establish the reality and specificity of immunocyte receptors⁶⁻⁹, and the strictness with which phenotypic restriction of immune pattern and immunoglobulin type holds¹⁰⁻¹².

The Two Component Approach

The next major development grew out of the recognition by Glick *et al.*¹³ that in chickens, antibody production was functionally dependent on the presence of the bursa of Fabricius in early life. In 1962, Warner *et al.*¹⁴ demonstrated that bursectomy resulted in a dissociation of immunological responsiveness, the capacity to reject homografts and to manifest graft-versus-host activity being retained. They also obtained evidence that the latter two responses were dependent on the presence of the thymus and raised the question whether any organ

functionally equivalent to the bursa of Fabricius existed in the mammal. This dissociation of thymus-dependent and thymus-independent immune functions was put on a firmer experimental basis by R. A. Good *et al.*¹⁵. They were the first to grasp the biological significance of genetic anomalies involving the immune mechanism in man^{16,17}. Not all such anomalies can be fully interpreted, and, as is the way with genetic disease, there are some puzzling variations within what seems to be the same syndrome. Nevertheless, Good's interpretation¹⁸ of congenital sex-linked agammaglobulinaemia Bruton type and the Di George syndrome, as representing at the immunological level "pure" failures to develop the thymus-independent or "bursal" system and the thymus-dependent system respectively, has been extremely helpful. The two component view can be described approximately as follows.

(1) The thymus-dependent system is responsible for providing the bulk of the circulating lymphocytes¹⁹, and functionally for homograft immunity and delayed hypersensitivity in their various forms. These include the sensitization brought about by application of simple chemicals to the skin²⁰ and the capacity to develop the typical syndrome of measles or chickenpox and to become immune thereafter. Absence of the system in Di George's syndrome²¹ is associated with susceptibility to infection by *Candida* and other fungal agents as well as to generalized atypical infections by vaccinia, measles or cytomegaloviruses^{18,22}.

(2) The thymus-independent system is responsible for plasma cell and antibody production, apparently including all the immunoglobulin types. Germinal centres are not seen in its absence²³. Other features of agammaglobulinaemia are normal thymic histology and a normal level of circulating lymphocytes, rejection of skin homografts and normal development of delayed hypersensitivity. Clinically agammaglobulinaemic children are intensely susceptible to bacterial infections of the lungs. Measles and chickenpox behave as in normal children²¹, but hepatitis can be lethal¹⁸. The significance of this dissociation in cellular and functional terms has been discussed²⁵.

Although the two-system picture is a useful one, there are still some minor discrepancies and difficulties which