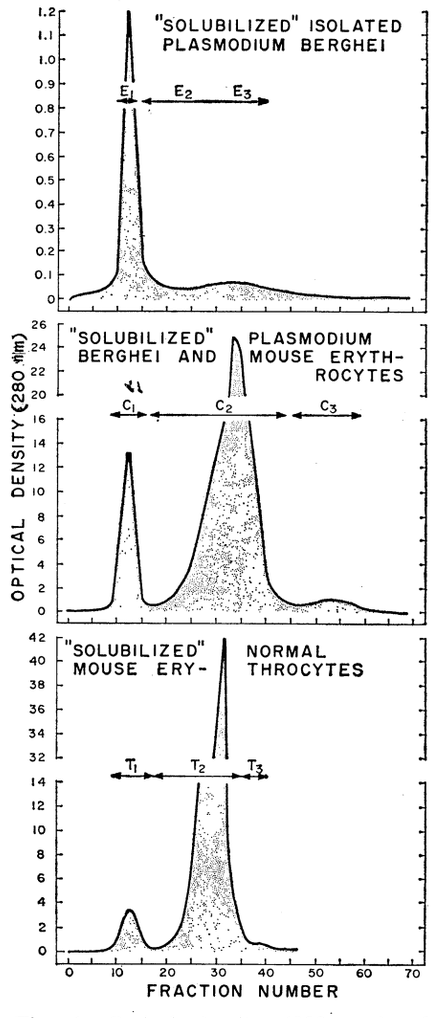

Fig. 1. Optical density (280 nm) of plasmodial fractions. (Top) Free plasmodia and plasmodial fragments; (center) infected mouse red blood cells; and (bottom) normal mouse red blood cells.

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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11. The protection induced by the unfractionated plasmodial materials in this group corresponds to that reported (*4*) for a much larger, similarly treated group in which 35 out of 39 animals showed a protective response.
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

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 disintegration 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

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 of these cognitive tasks, we measured the upper limit of the subject's capacity for each testing session.

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

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 $l(-)$-Δ^1-THC, with smaller amounts of cannabidiol and cannabinol. The oral doses used in this study, quantitatively calibrated according to the content of $l(-)$-Δ^1-THC, were 20, 40, and 60 mg of THC. The extract contained 20 mg of $l(-)$-Δ^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 $l(-)$-Δ^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) and then 1½, 3½, 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 (nondrug 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 nondrug 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, which occurred only under drug conditions. 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. Galenter, 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 equal to $\sim 10^{-17}$ cm^2. As possible candidates 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-