Excretion patterns of cannabinoid metabolites after last use in a group of chronic users

The urinary excretion patterns of 86 chronic cannabis users were examined after their last cannabis use by two common screening methods, the semiquantitative EMIT-d.a.u. and the qualitative EMIT-st (Syva Company). We demonstrated that under very strictly supervised abstinence, chronic users can have positive results for cannabinoids in urine at 20 ng/ml or above on the EMIT-d.a.u. assay for as many as 46 consecutive days from admission, and can take as many as 77 days to drop below the cutoff calibrator for 10 consecutive days. For all subjects, the mean excretion time was 27 days. Subject excretion patterns were clearly biphasic, with initial higher rates of excretion not sustained. During the subsequent period of leveling off, most subjects had one or more separate sequences of cannabinoid-negative urine test results, lasting a mean of 3 days each and followed by at least one positive result. Demographic, body type, and drug history variables proved to be only moderate predictors of excretion patterns. Findings were discussed in the context of potential clinical and forensic application. (CLIN PHARMACOL THER 1985;38:572-8.)

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Although it is generally agreed that delta-9-tetrahydrocannabinol (Δ9-THC) is the major psychoactive component of the cannabis (marijuana) plant, there are other cannabinoid constituents, as well as metabolites, that have psychoactive effects. One area of scientific interest is the lengthy retention time of the major metabolites, which seem to persist in the system for up to several weeks after repeated exposure. Very few studies have been made of the actual parameters and profiles of cannabis excretion. Lemberger et al.[1,2] reported that after intravenous injection, cannabis metabolites are excreted in the urine and feces for more than a week in both nonusers and chronic users. Hollister and Kanter[3] reported that a metabolite was found in the urine of nonusers for 72 hours after a single exposure. In the most extensive study to date, Dackis et al.[4] used the EMIT-d.a.u. (Syva Company) methodology in a locked ward setting and reported on seven heavy users who had positive urinalysis results from 14 to 36 days after their last known cannabis use.

We examined the urinary excretion patterns of chronic (regular) cannabis abusers after their last use. This investigation will provide data on the number of days that urine samples of chronic users produce cannabinoid-positive results and examine the various data elements that help establish the subjects' urine excretion patterns.

METHODS

Subjects. Our subjects were 86 male and female enlisted service personnel undergoing residential treatment for drug and alcohol dependence at the Naval Drug Rehabilitation Center in San Diego. Included in the study were arriving personnel with cannabinoid-positive urine samples for a minimum of the first 3 days after admission, drawn from a sample of 274 entering personnel that were tested over a 5-month period. Subjects were predominantly male (97.7%) and Caucasian (72.1%) and ranged in age from 18 to 34 years ($\bar{X}$ = 22.8 years). They had a history of marijuana use from 2 to 21 years ($\bar{X}$ = 8.9 years) and most (60.5%) used the drug once a day or more often. Over half (55.8%) were abusers of more than one drug, and almost one third (30.2%) were considered heavy users of one or more drugs besides marijuana.

Procedure. Subjects provided first morning voids under direct observation and precise chain-of-custody collection procedures. All urine samples were tested by

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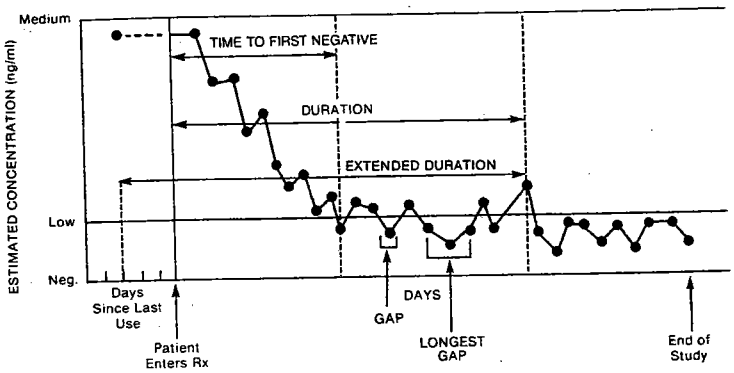

Fig. 1. Urine excretion pattern components: time to first negative result, duration, extended duration, negative gaps, and longest negative gap.

both the semiquantitative EMIT-d.a.u. and the qualitative EMIT-st (Syva Company) cannabinoid assays. Specific gravities, void order, and any prescribed medications were noted. Urine was collected daily until subjects had 10 consecutive cannabinoid-negative tests as determined by EMIT-d.a.u. Within the first week after arrival, data were collected in personal interviews for subject age, sex, body type (lean, average, obese), weight, and a height-weight integrated index (adapted from U.S. Navy combined standards). Self-reported data were also obtained on length of time since last use of cannabis before treatment entry; route of cannabis administration; amount administered during each use; history of cannabis use for lifetime, 6 months, 1 month, and 1 week before treatment entry; and history of alcohol and other drug use.

While it is impossible to state categorically that no marijuana could have been used by subjects while in the Center, the closely supervised conditions made this extremely unlikely. Subjects were never allowed to leave the facility for any reason without staff escort (total Center staff size was 150). Subjects were monitored by staff members 24 hours a day, 7 days a week, including every 15 minutes throughout the night. Subjects were singled out for special staff attention and urine results were carefully scrutinized each testing day and matched with staff clinical observations to reaffirm subject abstinence.

EMIT methodologies and equipment. According to the product literature, EMIT homogeneous enzyme immunoassays for cannabinoids are designed to detect a major urinary metabolite of Δ9-THC, 11-nor-Δ9-THC-9-carboxcylic acid, or a combination of one or more analyte equivalents such as 11-hydroxy-Δ9-THC, 8,β-hydroxy-Δ9-THC, or 8,β-11-hydroxy-Δ9-THC. The semiquantitative EMIT-d.a.u. assay system estimates metabolite concentration with a low or cutoff calibration of 20 ng/ml, a 95% detection level of 50 ng/ml, a medium calibrator of 75 ng/ml, and a detection range to 82.5 ng/ml (all results estimated to be ≥82.5 ng/ml are reported as 82.5 ng/ml). The amount of cannabinoids read from the calibration curve is approximate and expressed as analyte equivalents. The qualitative EMIT-st drug detection system identifies metabolite presence with a low or cutoff calibration of 100 ng/ml and a 95% detection level of 200 ng/ml.

Definitions. The cannabinoid excretion pattern was broken into five basic components: time to first negative result, duration, extended duration, number of negative "gaps," and length of the longest negative "gap" (Fig. 1). The time to the first negative result was defined as the number of cannabinoid-positive days after admission until a subject first produced a cannabinoid-negative urine sample. Duration was the number of days after admission, negative or positive, until the subject provided the last positive urine sample. Extended duration was the number of days in the subject's duration added to the number of days of claimed abstinence before admission to treatment. Number of negative gaps was defined as the number of times a pattern of cannabinoid-positive urine tests turned negative then returned positive. Length of the longest negative gap was the greatest number of days such a negative sequence lasted.

Data analyses. The excretion pattern for each subject was graphed for each method. Excretion outcome data were analyzed for the whole sample and for a by-group categorization based on self-reported light, moderate, or heavy cannabis use over the last month and last 6 months before admission. Wilcoxon two-sample rank tests were done to determine differences between the groups on urine test, demographic, and history vari-

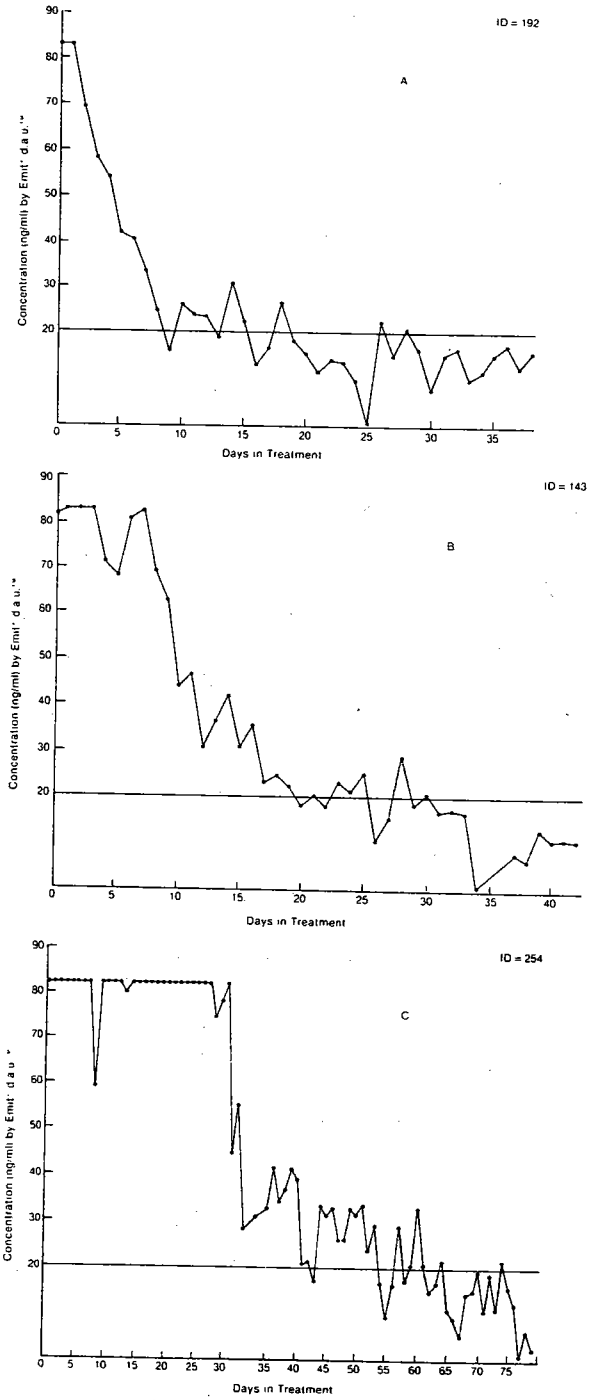

Fig. 2. Estimated daily urine level equivalents for three cannabis users. **A,** Light user; **B,** heavy user; **C,** heavy user.

ables. Pearson product-moment correlations were calculated to examine statistical relationships between variables. Because of the complexity of the study components, a stepwise regression procedure was determined to be best suited for an exploratory multivariate analysis.

RESULTS

Excretion patterns. Examination of the excretion patterns for the 86 study subjects by EMIT-d.a.u. showed substantial variations in form, slope, and number of days with cannabinoid-positive results. Representative subject excretion patterns are shown in Fig. 2. Patterns showed generally declining values after admission to treatment, with day-to-day fluctuations in estimated concentrations evident in most cases. Nonetheless, there were no obvious large peaks in the excretion patterns that suggested continued use during the Center stay. Inspection of the excretion graphs revealed a biphasic pattern. After a fairly steep drop in excretion levels, metabolite concentrations often fluctuated around the low or cutoff calibration level (20 ng/ml), causing prominent negative gaps in the graphs of both the EMIT-d.a.u. and EMIT-st results. There seemed to be no relationship between special events (i.e., extra physical exercise), medications taken, or weight loss and major shifts in excreted cannabinoid concentration.

Data were obtained primarily (91.2%) from the first void of the morning. Of the five subjects who provided two urine samples in the same morning, one showed an increase in estimated concentration between successive voids; the others showed estimated decreases of from 5 to 42 ng/ml as determined by EMIT-d.a.u.

Time to first negative result, duration, and extended duration. Table I shows descriptive statistics for the excretion pattern outcome variables for all subjects. For both testing methods, and especially for the more sensitive EMIT-d.a.u. procedures, subjects showed broader ranges and greater means than previously described in anecdotal reports or in the literature. When subjects were divided into light, moderate, and heavy use categories (Table I), the expected directional increases in these outcome variables were observed in most cases. However, there was substantial overlap in the ranges observed. Wilcoxon two-sample rank tests between groups showed significant differences for both methods in time to first negative result and in duration for only the light/heavy and moderate/heavy user comparisons. Extended duration was significantly different only for the light/heavy user comparison determined by EMIT-d.a.u.

Table II shows the frequency of duration of cannabinoid excretion patterns for both testing methods. When one considers the time it took to maintain negative results for 10 consecutive days, almost one third (32.6%) of the subjects (most of them heavy users)

Table I. Cannabinoid excretion patterns by EMIT-d.a.u. and EMIT-st methods: Overall and by intensity of use (light/moderate/heavy) in last month and last 6 months before treatment admission

	Time to first negative result (days)	*Duration (days)*	*Extended duration (days)*	*No. of negative gaps*	*Length of longest negative gap (days)*
All subjects (n = 86)					
EMIT-d.a.u.					
$\bar{X}$	16.0	27.1	32.0	2.6	3.4
SD	10.7	16.6	18.1	1.8	2.7
Range	3-46	3-77	6-81	0-8	0-10*
EMIT-st					
$\bar{X}$	4.3	9.2	14.1	1.0	2.7
SD	4.5	10.3	12.8	1.5	4.8
Range	0-22	0-45	1-55	0-8	0-26
Group 1: Light users (n = 8)					
EMIT-d.a.u					
$\bar{X}$	8.5	12.9	18.2	1.2	2.0
SD	5.2	10.3	10.3	1.8	2.7
Range	3-18	3-29	7-34	0-5	0-7*
EMIT-st					
$\bar{X}$	1.0	3.4	8.7	0.6	1.6
SD	1.5	4.2	5.1	0.9	2.4
Range	0-3	0-11	4-18	0-2	0-6
Group 2: Moderate users (n = 26)					
EMIT-d.a.u.					
$\bar{X}$	11.8	22.7	32.5	2.2	3.9
SD	7.4	13.0	19.2	1.5	3.3
Range	3-33	3-63	8-70	0-6	0-10*
EMIT-st					
$\bar{X}$	3.3	6.1	15.9	0.4	2.8
SD	3.2	8.9	17.1	0.8	6.4
Range	0-14	0-34	2-55	0-4	0-26
Group 3: Heavy users (n = 52)					
EMIT-d.a.u.					
$\bar{X}$	19.1	31.5	33.9	2.9	3.4
SD	11.5	17.4	17.7	1.9	2.3
Range	3-46	4-77	6-81	0-8	0-9*
EMIT-st					
$\bar{X}$	5.3	11.6	14.1	1.4	2.9
SD	5.0	10.9	10.9	1.7	4.1
Range	0-22	0-45	1-47	0-8	0-21

Light use is defined as cannabis use weekly or less often over the last month and six months preceding admission. Moderate use is defined as use two to six times per week in either time frame or averaged over the last month and 6 months. Heavy use is defined as use daily or more often in either the last month or 6 months.
*By operational procedures (see text), subjects were automatically terminated from the study after 10 days of negative EMIT-d.a.u. results.

remained positive by the EMIT-d.a.u. at 20 ng/ml for more than a month, with four subjects remaining positive for >2 months.

Number of negative gaps and length of longest negative gap. For both testing methods, there was a similarly wide range in the number of negative gaps (Table I). Negative gaps were noted in 87.2% of our subjects by EMIT-d.a.u. testing (75 of 86 cases) and in 47.7% of our subjects by EMIT-st testing (41 of 86 cases). Only a few of the demographic and history variables correlated with the number of negative gaps.

There was a wide range in the longest negative gap observed (Table I), with the Emit-st range of particular note. The length of the longest negative gap extended >3 days in 39.5% of our subjects as determined by EMIT-d.a.u. testing (34 of 86 cases) and in 24.4% of our subjects as determined by EMIT-st testing (21 of 86 cases). Of particular interest is that six subjects (7.0%) had a longest negative gap as determined by EMIT-st >10 days. It should be remembered that the length of the longest gap in EMIT-d.a.u. testing was limited by operational definition to only 10 days, the criterion for termination from the study.

Wilcoxon two-sample rank tests showed little con-

CLIN PHARMACOL THER
NOVEMBER 1985

Table II. Frequency distribution of the duration of excretion patterns as determined by EMIT-d.a.u. and EMIT-st

	EMIT-d.a.u.		*EMIT-st*	
Days	*No.*	*%*	*No.*	*%*
0	0	0.0	13	15.1
1-10	12	14.0	47	54.7
11-20	22	25.6	15	17.4
21-30	24	27.9	5	5.8
31-40	9	10.5	5	5.8
41-50	14	16.3	1	1.2
51-60	1	1.2	0	0.0
61-70	1	1.2	0	0.0
71-80	3	3.5	0	0.0

sistency in significant differences between groups in either the number of negative gaps or the length of the longest negative gap.

As expected, excretion variables correlated most highly with the other excretion variables (with r values ranging up to 0.89). Many of the history and demographic variables were also significantly related to the excretion variables, but the correlation coefficients were considerably smaller (with r values ranging up to 0.44) than those observed between the excretion variables themselves.

When all variables were placed in the stepwise regression procedure with time to first negative result, duration, and extended duration, the excretion outcome variables proved to the greatest predictors, accounting for between 72.1% and 100.0% of the variability. When the excretion outcome variables were removed, the 12 demographic and history variables selected for evaluation were only modest contributors to a predictive model, either singly or in complement (Table III). For the EMIT-d.a.u., although the overall hypothetic models were significant ($P < 0.001$), the percent of variability accounted for by variables in the time to first negative result, duration, and extended duration regressions were relatively slight (35.7%, 42.7%, and 48.3%, respectively). Similar results were seen in the EMIT-st analyses, with the variables in the time to first negative result, duration, and extended duration regressions accounting for 41.4%, 31.8%, and 59.2% of the variability, respectively, despite overall significant models ($P < 0.001$). Three of the demographic and history variables (age, weight, and having a history of cannabis use more than once a day) seemed to be the most prominent, but their overall predictive value could only be judged as moderate.

DISCUSSION

Despite considerable clinical and forensic interest, there have been surprisingly few published data on the length of cannabinoid excretion in the urine of chronic users after last use. Important data were provided by Dackis et al.,[4] whose seven subjects had a mean of 24 days with cannabinoid-positive results (with an upward range of 36 days) before a first negative result was observed. A published case study[5] gave data on a chronic smoker who provided cannabinoid-positive urine samples for 15 consecutive days after reportedly ceasing use, and who was still positive after 20 days of testing. (Both of these studies used EMIT-d.a.u. testing with a 20 ng/ml cutoff.) Our results are in general agreement with those data and substantially extend the published findings. Urine samples from our 86 chronic users were still cannabinoid positive up to 46 days ($\bar{X}$ = 16 days) as determined by EMIT-d.a.u. before the first negative result, and took up to 77 days ($\bar{X}$ = 27 days) to drop below the 20 ng/ml cutoff for 10 consecutive days (Table I). Both the extended range of positive days and the variations in the excretion outcome variables for both EMIT-d.a.u. and EMIT-st were unexpected and not previously reported.

Our study validates the reliability and usefulness of the EMIT-d.a.u. method for determining urinary excretion patterns after chronic cannabinoid use. Our results also provide new information that should be taken into account in the interpretation of urine test results for cannabinoids, regardless of the method used. Current applications of urinalysis, such as in surveillance of identified users, should be reevaluated in light of our data.

Our data generally confirm previous research that chronic users can take, on the average, about a month to achieve consistently negative urine samples as determined by a sensitive urine assay such as the EMIT-d.a.u. that uses a 20 ng/ml cutoff calibration (Table I).

In terms of the duration of positive results, well over half (60.6%) of our chronic users had cannabinoid-positive results for ≥21 days after last use, almost one third (32.7%) had positive results for >30 days, and 4.7% had positive results for >60 days before dropping below the EMIT-d.a.u. 20 ng/ml cutoff for 10 consecutive days (Table II). There was a natural break observed in the distribution at 50 days, which based on these data seems to be a reasonable upward limit for the evaluation of most chronic users (Table II). The five subjects who had positive results for >50 days had been heavy users for at least 12 years; however, there were

Table III. Contribution of index history variables to predicting excretion pattern outcomes*

EMIT-d.a.u.				*EMIT-st*			
Index variable	*Cumulative r^2*	*Contribution to outcome (F value)*	*P value*	*Index variable*	*Cumulative r^2*	*Contribution to outcome (F value)*	*P value*
				Time to first negative result			
MJ use in last week†	0.183	7.63	0.008	MJ use in last week	0.186‡		
Age	0.268	6.02	0.017	Age	0.292	11.54	0.001
History of MJ use more than daily	0.321	5.48	0.023	History of MJ use more than daily	0.339	6.35	0.015
Weight	0.357	3.17	NS	MJ use in last month†	0.369	13.18	0.001
				Weight	0.414	6.54	0.013
				Duration			
History of MJ use more than daily	0.184	8.14	0.006	Weight	0.141	12.29	0.001
				History of MJ use more than daily	0.274	11.06	0.002
Weight	0.305	13.29	0.001				
MJ use in last 6 months†	0.346	6.54	0.013	Age	0.318	3.73	NS
Age	0.396	6.42	0.014				
Days since last use†	0.427	2.97	NS				
				Extended duration			
Days since last use	0.120	10.23	0.002	Days since last use	0.375	43.66	0.001
History of MJ use more than daily	0.273	8.14	0.006	Weight	0.464	13.56	0.001
				History of MJ use more than daily	0.543	5.92	0.020
Weight	0.381	13.29	0.001				
MJ use in last 6 months	0.423	6.54	0.013	Age	0.575	5.43	0.020
Age	0.483	6.42	0.014	MJ use in last 6 months	0.592	2.30	NS

MJ = Marijuana; NS = not significant.
*Stepwise multiple regression evaluating 12 index history variables including age, physical characteristics (weight, height-weight index, body type), and recent and long-term patterns of marijuana use (n = 61).
†Before admission to treatment.
‡Contribution of variable before being removed by stepwise regression procedure.

other subjects with similar cannabis histories who had cannabinoid-positive results for <50 days.

Of those chronic users who had a cannabinoid-positive result on the EMIT-st, only a few (15.1%) had positive results on the EMIT-st for ≥21 days, while a majority (64.4%) had positive results for ≤10 days before returning to a consistently negative pattern (Table II).

Although there were statistically significant differences in the means of many of the excretion variables between subjects grouped by self-reported light, moderate, and heavy use, the amount of overlap in the ranges was noteworthy. While it is not clear how individual data points would be affected by urine samples collected randomly during the day, the outside ranges could aid in the interpretation of test results. Thus if a subject claimed to be a light user, one would expect to see a first negative test result on the EMIT-d.a.u. within approximately 18 days after ceasing use and the daily test results to start being consistently negative no more than a month after last use.

Although many were statistically significant, few of the demographic and history variables showed substantial correlative relationships with the excretion pattern components. Based on the stepwise regression analysis, demographic and history variables showed little usefulness as predictors of excretion patterns (Table III). There was a lack of real predictive prominence of body type, weight, and height-weight index, despite suggestions of previous research in animals.[6] Weight alone seemed to show the most promise. Age was evident in almost every regression; however, its overall importance appeared relatively small. Also demonstrating little impact were the various cannabis history variables.

Although expected, the identification of a clear biphasic pattern in urine has not been previously reported in the literature on cannabinoid excretion. Also of interest is the fluctuating effect in the day-to-day EMIT-

d.a.u. determinations, especially around the cutoff level that created the strings of negative gaps. This phenomenon is not too surprising for a long-persisting analyte, but might tend to confuse the proper interpretation of results for those not familiar with this phenomenon. This can be partly attributed to the semiquantitative nature of the assay and the differing reactivity with the metabolites, to differing amounts of the metabolites being released in the body, and to increased test variability when measuring values at the extreme end of the calibration curve. Once a subject had a urine test result that went below the 20 ng/ml cutoff, no subsequent test ever went above the medium calibrator (75 ng/ml) and only five subjects (6.7% of the subjects with negative EMIT-d.a.u. gaps) had positive urine samples >50 ng/ml.

Estimates of time since last use derived from a single urine test result or even a spaced series of results would seem to have limited forensic value. Our study reaffirms that a positive urine test result from a chronic user does not necessarily indicate recent or continued use. Because of large individual variability, a positive test result may reflect use within the past few hours, days, weeks, or even months, depending on the cutoff calibration level selected. Because of the special sensitivity demonstrated by the EMIT assay, which cross-reacts with a broad metabolite mix rather than a single prominent metabolite such as the 9-carboxy-THC (COOH-THC), it is clear from previous comparative research that the duration of positive results would also be affected when an alternate method is used.[7,8] Additionally, some urine specimens have been found to have lower concentrations of free COOH-THC than expected based on unpredictable rates of metabolization to its glucuronide ester.[9-11] Even EMIT results must be interpreted with some small amount of caution because assay response may vary slightly with the relative ratio of free COOH-THC and this unstable glucuronide conjugate.* Finally, the impact of the differences of drug potency (plant genetics), the potential interactive effect of previous alcohol and other drug abuse, and the differences in bioavailability of Δ9-THC in the route and pattern of administration due to the experience of the user would seem important, but such studies were beyond the scope of our investigation.

*Willette RE: Personal communication, 1985.

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