

73SB-711

June 19th, 1973

Dr. Costas Stefanis,
Professor of Psychiatry,
University of Athens School of Medicine,
Eginition Hospital,
7th, Vasillissis Sophias Av.,
Athens, Greece.

Dear Costas,

I have been informed by the National Institute of Mental Health that they do indeed have 2.5% THC-A-9 marijuana. I am requesting it to be shipped to me today and at the same time am requesting a BNDD export permit. It is my expectation that I should have most of this material within two weeks and should then be able to ship it to you. I plan to ship the material under your import license 12410, as I have requested 500 grams cannabis (marijuana) from the U.S. government agency, the National Institute of Mental Health.

My best regards.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MP/1j
Enc.

P.S. I have cancelled check #1271, dated April 10, 1973. Enclosed is a replacement for that check. If you find the original, please destroy.

73SB-700

June 15th, 1973

Costas Stefanis, M.D.,
Professor of Psychiatry,
University of Athens School of Medicine,
Eginition Hospital,
74, Vasillissis Sophias Ave.,
Athens, Greece.

Dear Costas,

I very much enjoyed our visit and was very much impressed by the extent and quality of the work that you and your associates have done.

Enclosed is a review of the budgetary allowances, the amount paid to date, and the balance to the end of the year. It is permissible to transfer funds from one category to another except that equipment may not be bought and that travel expenditures may not exceed the allowances given.

I have spoken to Dr. Szara about the high concentration marijuana. At first, he felt that hashish should be used, but after some discussion we agreed that a high dose marijuana would be acceptable. I called Mr. Boyer, who is responsible for the NIMH supplies, and he is checking the availability of a high concentration. Meanwhile, he has sent you 40 additional bottles of 1.8% marijuana using your import certificate 12410 and an export license from NIMH. I am to call him early next week and if higher concentration supplies can be obtained he will get them. In the meanwhile you should check the 1.8%, and if that is unsatisfactory, perhaps you could check with Dr. Miras about a supply of high concentration hashish.

Separately, I am sending you the outputs which I failed to bring with me, as well as an analysis of a manic depressive patient which Tom asked me to do for him.

Costas Stefanis, M.D.

-2-

June 15th, 1973

As soon as we have obtained the additional data sheets, we will do the analysis we discussed, as well as review the post-smoking EEG data.

There were some other things that I should do and I shall attend to them in the coming week. For the meanwhile, my best wishes.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF/ij
Enc.

6/12/73

Budget - Subcontract (Greece) - 42-70-98

	<u>Allowed</u>	<u>Paid to 4/1/73</u>	<u>Balance to 12/31/73</u>
a. Stipends	\$88,400	\$56,751	\$31,649
b. Volunteer fees	12,300	10,354	1,946
c. Hospitalization	1,850	0	1,850
d. Telephone, postage	600	40	560
e. Lab. analysis	7,000	4,500	2,500
f. Material & Supplies	3,530	2,112	1,418
g. EEG recording	3,310	1,690	1,620
h. Travel	3,921	328	3,593
i. Consultation, services	16,980	1,680	15,300
	<u> </u>	<u> </u>	<u> </u>
Total	\$137,891	\$77,455	\$60,436
	<u> </u>	<u> </u>	<u> </u>

73E-673

May 17th, 1973

Costas Stefanis, M.D.,
Professor of Psychiatry,
University of Athens School of Medicine,
Eginition Hospital,
74, Vasillissis Sophias Av.,
Athens, Greece.

Dear Costas,

I have made arrangements to arrive in Athens from Amsterdam on Tuesday afternoon, June 5th, and have made a reservation to stay at the Grand Britannia. I should like to meet with you either that evening, or any time during the next two days. I should like to be able to review the data which I will be bringing with me with you and your associates; the subcontract extension; and to work with you in planning the withdrawal study.

I have written to Steven Szara to tell him the time that I will be in Athens, because he has been particularly interested in the next phase of the program. Should he be able to join us, it would be most valuable, and I have extended an invitation to him.

I look forward to seeing you.

My best regards,

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF/ij

73I-651

April 27, 1973'

Costas Stefanis, M.D.,
Athens University Medical School,
Department of Psychiatry,
Eginition Hospital,
74, Vasilissis Sophias Av.,
Athens, Greece.

Dear Costas,

Whenever I sit and think of writing to you the popular song from '1776' - "Is anyone listening, is anyone there?" comes to mind.

Separately, I have sent by air a package containing a manual of statistical programs and a tape which contains these programs on seven tracks at the appropriate BPI.

We have been asked to come to Washington on May 2nd to negotiate the extension of the contract. I am assuming that the funds requested in our letter of March 15th met with your approval, and we will do our best to obtain full approval.

I am enclosing a copy of a memorandum given me by Rhea which tells you about the status of our calculations.

It is advisable for us to review the progress of the last few months and to make the necessary plans for the continuation of the withdrawal phase and the summary of the data of this interesting study. Should you wish to come to the United States within the next six weeks, I would be glad to work with you here. Should this not be feasible, I would then suggest that you let me know what is optimal for you, and I will try to come to Athens.

My best regards.

Sincerely yours,

Max Fink, M.D.
Executive Director

MF/ij
Enc.

73I-556E

March 5th, 1973

Dr. Costas N. Stefanis,
Athens University Medical School,
Department of Psychiatry,
Eginition Hospital,
74, Vasilissis Sophias Ave.,
Athens, Greece.

Dear Costas,

We are progressing very well with the EEG data. Because of some absent records, we have done the regression analyses on 16 subjects, and this seems to be adequate to give us good data for the differences between the various conditions. The behavioral data which Rhea brought back with her has been coded and correlations between the EEG and the behavioral information are now in progress - some having been completed during the last few days.

Rhea has called Washington on a number of occasions during the past week, but we do not have any more information. If I do not have a clear response by March 10th, I will call, and if there is no answer by the 15th, I will call you. A copy of Rhea's report to me which we have filed with Dr. Szara is enclosed.

My accountant has been over the receipts which Rhea brought with her. This documentation is adequate. Enclosed is our check for the four invoices of January 6th.

In order to obtain an export license, it is necessary to file a whole set of documents - which I did on March 1st.

Rhea came back most enthusiastic regarding the content of the work, as well as the cooperation which she received. Many thanks.

My best regards.

Sincerely yours,

Max Fink, M.D.
Executive Director

MF/ij
Encs.

73I-513I

February 1st, 1973

Costas Stefanis, M.D.,
Professor of Psychiatry,
University of Athens School of Medicine,
Eginition Hospital,
74, Vasillissis Sophias Av.,
Athens, Greece.

Dear Costas,

Enclosed are checks in the amount of \$13,365 to cover the salaries for April-June, 1972 and October-December, 1972. I will need the cancelled checks for these salaries as well as the ones issued for July-September.

Copies of the expense vouchers for \$1,140 are also necessary.

I am returning the other voucher requests and ask that these be re-done. I have made suggestions on each, which will allow me to meet the requirements of the auditors.

You should know that in our first year, we were allowed some overhead for the expenses in Greece, and should there have been disallowances, we could fall back on these funds. Since June 25, 1972 we have been denied an overhead allowance. We considered cancelling the contract but our interest in the study impelled us to accept a bad contract. (Indeed, if I were not personally involved, the Directors would have rejected Washington's offer). To protect my Board, we must have adequate records.

You will recall that you rejected direct payment of your personnel, using national pride and your need to relate to the staff as levers. I accepted your wish, as I accepted the NIMH demand for a no-overhead contract, to accomplish the mission. But, the risk to the Association is too great and unless we obtain adequate statements, checks, etc., we cannot continue this contract.

As Rhea will tell you, I am too fatigued with contesting with NIMH, and a threat of loss of money for so little gain that I am unenthusiastic about continuing the contract after June 25, 1973. I have applied to NIMH for an extension, so as not to jeopardize your chances, and will endeavor to support these

Costas Stefanis, M.D.

-2-

February 1st, 1973

studies, but your cooperation is critical - in the financial arrangements and in the protection of the interests of my associates.

Rhea has been briefed and will try to amplify these issues.

Sincerely yours,

Max Fink, M.D.

MF/1j
Encs.

February 1st, 1973

Costas Stefanis, M.D.,
Professor of Psychiatry,
University of Athens School of Medicine,
Eginition Hospital,
74, Vasillissis Sophias Av.,
Athens, Greece.

Dear Costas,

Rhea, Voita, and I have read your summary report, and found much of interest and significance. We reviewed each of the sections and our comments and suggestions have been noted by Rhea who will review these with you in Athens. My own notes, which she will amplify, are attached.

I have asked her to review the following technical issues with you.

(1) The report has been sent to Dr. Robert Petersen, at NIMH. I believe the data is sufficient for their review and decision as to any continuation or extension. While I have reminded them of our agreement, I am not sanguine that they will be able or willing to move with any alacrity; and would suggest that, should you wish to continue this interesting type of work, that alternate sources of support be sought. I have discussed these with Rhea and she is prepared to assist you.

(2) Both the report in August and this report take little cognizance of the contribution of my associates to the studies. Recognition of contributions is always a delicate issue and when we discussed this in Copenhagen, I trusted to your judgement to protect the interests of the staffs involved. This report seemed deficient in this regard and I have made some amendments, which I trust will meet your approval.

(3) We have reduced all the EEG tapes by period analysis, and have 16 subjects complete with 5 experiments each. The initial processing has been done using our linear regression analysis model. The drug conditions are distinguishable from placebo, in patterns similar to that reported by Volavka and Dornbush in their earlier studies in U.S. volunteers at lower doses. The analysis was done, including the post-smoking period and the post-testing EEG in a single analysis. As the variability is high post-testing, additional analyses are in progress using a quadratic regression model, for the first post-smoking period. In addition, we are carrying out some special analyses to amplify the changes in the alpha bands.

February 1st, 1973

These data should be complete in two weeks. We would like to undertake correlative studies, of the EEG, heart rate, self-reports, and some task performance data. Volavka has used a "forced regression" analysis model for our heroin and cannabis data with success, and we propose some similar studies here. Rhea has a list of subjects and data which we will need to carry out these analyses.

(4) As I have written to NIMH and discussed with you, the findings of these studies are of considerable interest and we must give thought to both the mode and time of presentation. We have discussed the question and Rhea will discuss the enclosed memorandum of our suggestions, and hopefully we can outline a set of steps which can accommodate our mutual contributions and needs.

Rhea is bringing the battery you requested, as well as some cannabis material. On her return, we would like to send samples of hashish, and residual marijuana and THC- Δ -9 to NIMH for assay, and I would appreciate your making these small samples available.

(5) The initial thrust for this study was the observation of EEG slowing reported by Professor Miras. The EEG records of the hashish smokers were examined by 4 neurologists, and the controls by 2. But, a critical reviewer could argue that the observers knew which records came from hashish smokers and which from controls. Perhaps, it would be worth the effort and cost to code the 60-70 records and ship these to an independent, experienced electroencephalographer of known reputation for a detailed report? Rhea has some suggestions for candidates in the U.S. and Europe.

(6) There are problems in our book-keeping which is of the following nature. The auditors will require "back-ups" that the salaries were paid as specified; and that the expenses for supplies were paid. I believe you are depositing our check and issuing your checks for the expenses. I need the processed check or its copy for salaries; and the bills with checks for other expenses. If cash, your initials or one of your staff certifying a cash payment should be satisfactory.

Again, my congratulations on a fine report and my best regards to Adele and your associates. I look forward to seeing you soon.

Sincerely yours,

Max Fink, M.D.

MF/ij

Suggestions for Presentation

A. Separate Reports

1. (a) A social, medical, neurological summary of the two population samples, with emphasis on the social characteristics, smoking history, work and family characteristics. Including a history of the sample. Stefanis, Boulougouris, Gefou, Liakos
- (b) A description of the medical aspects - physical examination, mental status, EEG (clinical), Echo-EEG, pulmonary. Stefanis, Liakos, Tom, etc.
2. Psychological Characteristics of the two populations - I.Q., WAIS subtests and profile, memory tasks. Dornbush, Kokkevi
3. Acute Experiments
 - (a) Design, goals, dosages used, with types of psychiatric response, case descriptions. Stefanis, Boulougouris, Dornbush
 - (b) EEG and heart rate; relations to each other and to self ratings; tolerance? Volavka, Tom, Fink & Stefanis
 - (c) Psychological test data; EP, pupils, etc. Kokkevi, Liakos, Dornbush
4. Tolerance Development: letter to JAMA. Fink, Stefanis
5. EEG effects (brain effects) of chronic hashish - letter to editor. Stefanis, Tom, Fink, Volavka

B. A single Volume

1. Introduction
History of study; Aims.
Fink
2. Chemistry of hashish; history of hashish use in Greece; history of sample.
Miras

Suggestions for Presentation (Continued) - 2

- | | |
|--|----------------------|
| 3. (a) Sample of users | Gefou |
| Identification | Gefou |
| Social | Gefou |
| Medical | Liskos |
| Neurophysiological | Tom, Volavka |
| Psychological | Kokkevi, Dornbush |
| (b) Sample for control | Stefanis |
| (c) Comparisons | Stefanis |
| 4. Acute Experiments | |
| (a) Goals, design | Stefanis and Fink |
| (b) History; methods; description
of subjects; drop-outs
smoking times, interview
behavior. | Stefanis |
| (c) Psychological and performance
tasks. | Dornbush and Kokkevi |
| (d) EEG, heart rate. | Tom and Volavka |
| (e) Chemistry of substances. | Miras |
| (f) Significance for drugs,
tolerance, interactions of
components. | Fink, Stefanis |
| 5. Withdrawal Experiments. | Stefanis |

Questions from Report of January 25, 1973

1. Control Sample

Table 2. Why were patients admitted to hospitals?
Any relation in time to smoking hashish?

Employed: were there differences in types of jobs?
What factors could contribute to the difference
in two groups in rate employed?

Page 17. Should EEG records be reviewed by independent
EEG'er using coded records?

The STM and WAIS differences are troublesome.
If they reflect effects of drug use, they would
reflect brain changes - do we have other
differences? If not, how much weight is to be
given to these solitary findings?

2. Testing of Substances

Page 21. The anecdotal statements about #7 are important
reflections of tolerance. How long does it take
the men to develop tolerance? This man, were he
to be tested again, could give an idea (assuming
he is using hashish).

31. Would not an analysis of covariance be a better
model, since subjects differ widely as to starting
levels? (see Diagram II - page 33). This is clear
in diagrams IV and V, where dose effects and initial
level seem to interact.

38. This critical graph reflects one of the principal
effects of cannabis. If the graph is correct 78 mg
THC as marijuana has a great an effect as 160 mg
THC as hashish. What are the significant
relationships? $A = B = C \neq D$
(or) $A = B > C > D$
The heart rate effect also persists for much longer
than anticipated. Are A, B, and/or C still $> D$
at 10, 15, 20 minutes post-break (= 75 minutes post-
smoking).

40. Are these to be interpreted as the result of HV and
not drug related?

Questions (Continued) - 2

42. Self ratings follow our THC content. To what extent did subjects know (or guess) what they were getting? Are these data sufficiently consistent or reliable to allow some conjectures that self-rating is related to dose of THC-A-9 while heart rate is not?
47. What is "fault index"?
48. Are we to interpret these as drug effect at 30' and practice effect (or loss of drug effect) at 70'? Here, too, response is related to THC content.
50. Data for E included. Is it available for other tests as well?
- 53-55, 56. Behavioral responses seem most marked in a few subjects: 40, 34. In 24, 35, 38, and 41 there is a response to placebo as well. Is there any clue in personality or amount of smoking done in 34 and 40 to relate to the severe response?

Questions (Continued) - 3

A.	5	18	(24)	(34)	37			
B.				32	(35)	(38)	(41)	(40)
C.								(40)
D.			(24)		(35)	(38)	(41)	
E.				(34)		(38)		(40)

Continued Support

1. Ford, Rockefeller, FFRP, Howard Samuels, Dreyfus.
2. Greek funds - Onassis.
3. IBRO - WHO.

Suggest Stefanis and Miras decide if study is worthwhile and plan to approach foundations with these pilot data.

If he wishes U.S. intervention, needs an agreement between Dornbush (who will have to go to agencies) and himself; or Freedman and Dornbush.

Suggest project leave NIMH and seek more "independent" and 3 year support.

Grice

- (1) Complete report 1st phase
- (2) ~~Exp~~ Control group
- (3) Data collected - 12 subjects
Completed to 10/12/72
- (4) Plans
 - ① Complete 2^o - Data analysis
 - ② expand comparison group

Robert C. Petersen, Ph.D.
Chief, Center for Studies of Narcotic and Drug Abuse
National Institute of Mental Health
5600 Fishers Lane
Rockville, Maryland 20852.

Dear Bob:

material sent to us by Dr. C. Stefanis
We are enclosing ~~the October 15th quarterly progress report~~. This represents the October 15th quarterly progress report of contract HSM 42-70-98. This report ~~concerns~~ includes a summary comparison of hashish users and controls. A detailed ~~report~~ profile of the hashish users was included in the report sent to you in August. Thus this paper represents the addition of controls which were ~~absent~~ ^{missing} at that time.

28

An elaboration of the characteristics of the control population ~~will be included~~ and detailed comparison with hashish smokers will be the subject of the January 15 progress report.

RL

Had -	36 + 26	5.4%	150, 100 mg THC
MS	36	2.6%	75 mg
THC	100 mg		100 mg THC

See 9 member to Green & Inc

THC-Δ-9