A double-blind provocative study chocolate as a trigger of headache

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Cephalalgia

Marcus DA, Scharff L, Turk D, Gourley LM. A double-blind provocative study of chocolate as a trigger of headache. Cephalalgia 1997;17:855–62. Oslo. ISSN 0333–1024

A provocative double blind study of headache was performed using chocolate as the active agent and carob as the placebo. The chocolate and carob samples were formulated to duplicate products used in an earlier study (1) in which strong differential effects between the ability of chocolate and carob to trigger headache in migraine were shown. Sixty-three women with chronic headache (50% migraine, 37.5% tension-type, 12.5% combined migraine and tension-type) participated in the study. After 2 weeks of following a diet that restricted vasoactive amine-rich foods, each subject underwent double-blinded provocative trials with two samples of chocolate and two of carob presented in random order. Diaries were maintained by the subjects throughout the study, monitoring diet and headache. The results demonstrated that chocolate was not more likely to provoke headache than was carol in any of the headache diagnostic groups (^{2}(2) 0.36, p=0.83). Interestingly, these results were independent of subjects' beliefs regarding the role of chocolate in the instigation of headache (^{2}(1)=0.73, p=0.39). Headache diagnosis and the concomitant use of additional vasoactive amine-containing foods were also not associated with chocolate acting as a headache trigger. Thus, contrary to the commonly held belief of patients and physicians, chocolate does not appear to play a significant role in triggering headaches in typical migraine, tension-type, or combined headache sufferers.

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A wide variety of foods have been implicated as possible triggers for migraine, with chocolate among the most frequently cited culprit (2, 3). The presence of vasoactive amines related to serotonin (5HT) and norepinephrine (NE) in these foods is believed to be involved in provoking headache (4–6) through either directly affecting blood vessels (7, 8) or by having an indirect effect by causing the release of epinephrine (EP) and NE (9).

A variety of amines have been implicated in the development of headache, most commonly tyramine (TYR), histamine (HIS), and beta-phenylethylamine (PEA).

Cheeses (especially Camembert, Cheddar, and Parmesan), peanuts, meats (especially pork and venison), and alcohol, are known to contain TYR, HIS, and PEA, and citrus fruits contain octopamine and synephrine. Each of these foods has been implicated clinically to be causally related to headache activity. Recently, another vasoactive amine, spermine, has been identified as an important transmitter of pain (10), although the role of spermine in headache is unknown.

One of the most commonly cited food triggers of headache is chocolate (13, 14). Chocolate is especially rich in a variety of vasoactive amines including PEA, which crosses the blood-brain barrier (11) and effects cerebral blood flow (12, 13) [although this has been disputed (14)]. PEA is metabolized by monoamine oxidase (MAO), and headache may be related to a deficient metabolism. Sandler et al. (15) reported reduced oxidative capacity of MAO for PEA in migraineurs, and identified a headache occurrence rate of 50% in migraine headache patients exposed to PEA, compared to 6% of those receiving a placebo. Glover et al. (16) also observed a reduction in MAO activity during migraine attacks.

Despite the beliefs of many physicians and headache sufferers, evidence for the role of vasoactive amines as precipitants of headache is mixed (17). Only 22 to 45% of headache sufferers identify foods as triggers (18, 19), and it is unclear why only a limited proportion of headache patients are affected. Moreover, researchers have suggested that the percentage of headache sufferers who actually have food triggers is significantly less than the percentage who identify food triggers (20). For those that do identify foods as triggers, some vasoactive amine-rich foods may be identified as consistent headache triggers, whereas others are not.

This suggests that, if food acts as a headache trigger in some individuals, vasoactive amines may not play as strong a causative role as once thought. For example, although red wine was thought in the past to be a trigger for headache because of its TYR content, more current research implicates flavanoid phenols as the headache-provoking agent (21).

Similarly, PEA may not be the strongest headache trigger in chocolate. Theobromine, a methylxanthine found in cocoa that is similar in chemical structure to caffeine (22), may act as the headache trigger.

The supposition that diet plays a role in triggering headache has been both supported (23, 24) and challenged (20, 25, 26). Hannington and colleagues conducted a series of double-blind challenges of both TYR capsules and chocolate, and found that the TYR and chocolate were related to headache onset, whereas the placebo was not (9). Some dietary restriction studies have reported a decrease in headache after participation in an elimination diet (3, 27). In contrast, other studies have found that dietary restriction does not significantly decrease headache (29), or that placebos are as likely to result in headache as challenge foods (28, 30). It has been suggested that subject selection plays a large role in the outcome of these studies (29). The Hannington studies, for example, included only those headache sufferers who both identified specific foods as headache triggers and as a result avoided consuming those foods. Although many headache sufferer will implicate certain foods as causative agents for headache, only a small percentage actually change their diet to avoid those foods.

Prospective studies investigating the effects of chocolate ingestion on migraine headache have found disparate results. Hannington (9) reported that the ingestion of chocolate resulted in migraine headaches in all six of the patients in her sample, while a sample of chocolate with the amines removed resulted in no headaches. Gibb et al. (1) compared chocolate with a carob-based placebo in 20 migraine headache patients, and found that 42% of the group ingesting chocolate reported experiencing a headache, compared to no reported headaches in the group that ingested the carob. [Chocolate and carob are chemically dissimilar (30), and carob does not contain PEA.] In contrast, Moffett et al. (33) conducted a similar study with 25 migraineurs and reported headaches in 19% of the chocolate group and 12% of the carob placebo group.

Traditionally, migraine is considered to be fundamentally dissimilar from tension-type headache, and migraine sufferers are thought to be more sensitive to food triggers. Several studies, however, have described similarities between migraine and tension-type headache in clinical symptoms (31), pathophysiology (32, 33) and effective treatments (34, 35) [for a review, see Marcus (36)]. In addition, the same triggers identified by migraine sufferers are identified by tension-type and combined headache patients (13). Chocolate has been identified as a trigger in 22% of all chronic headache sufferers. This suggests that chocolate should be tested as a provocative trigger for headache diagnoses other than exclusively migraine.

All three of the chocolate challenge studies reviewed above were conducted with small patient samples diagnosed with migraine, and all of these subjects had identified various foods as triggers for their headaches prior to their participation in the studies. It is not known what percentage of a patient sample in which patients have not specifically identified themselves as food-sensitive will find chocolate triggers their headaches. Neither is it known if chocolate specifically triggers migraine or if it may act as a trigger for other types of chronic headache.

In summary, chronic headache may be triggered by a variety of foods, including chocolate. Challenge studies have demonstrated conflicting results, with some clearly associating chocolate ingestion with headache, and some finding no association whatsoever Whether chocolate specifically triggers migraine, or triggers other related headaches, such as tension-type, has not been investigated. The present study was designed to evaluate whether chocolate provokes headache in a large sample of headache sufferers with migraine, tension-type, or combined migraine and tension-type headache.

Patients and methods

Chocolate and carob product development

The chocolate and placebo recipe formulas were obtained from a previously published article that demonstrated chocolate was a trigger of chronic headache (1). Both the chocolate and carob bars were manufactured by the American Cocoa Research Institute. The samples were identical in appearance and wrapping. Each sample weighed 60 g. [Gibb et al. (1) reported that headaches were triggered in their headache patient sample with 40 g chocolate bars.] In order to ensure the blinded condition of the subjects, both chocolate and carob products were supplemented with mint flavoring to mask natural differences in taste. Both products were tested to determine biogenic amine content to determine whether these samples were chemically similar to previously published reports of amine levels in cocoa products. In addition, internally standardized gas chromatography/mass spectrometry was used to detect theobromine and caffeine content of the samples.

A convenience sampling of 21 adults (10M, 11F; mean age 37.0 years) working in a healthcare facility were recruited for a double-blind taste test of the chocolate and carob products to determine if they were able to identify which sample contained the actual chocolate product. Subjects ate approximately 7.5 g of both a chocolate and a carob sample on two different days, with most subjects eating the samples one day apart. At each testing, subjects were asked to record whether they believed they were eating chocolate or not. Subjects guessed that they were eating chocolate 66.7% of the time, and a kappa statistic was not significant ($k=0.19$, $p<0.20$), demonstrating that subjects could not accurately determine what they were eating. Thus, the samples appeared to be adequate for use in the subsequent trials.

Provocation study

Women with recurrent headache were recruited through posters placed across the main branch of the University of Pittsburgh campus. Only women were recruited because: (i) females have been demonstrated to be significantly more likely than males to report that foods trigger their headaches; and (ii) the majority of headache sufferers are women (14). All subjects received a neurology evaluation from a board-certified neurologist and were given a diagnosis according to the criteria of the International Headache Society (IHS) (37). Subjects were also given a set of self-report questionnaires to complete including the Multidimensional Pain Inventory (MPI) (38), the Headache Locus of Control scales (HALOC) (39), and the Center for Epidemiological Studies depression scale (CES-D) (40). These questionnaires were used to compare the study sample with previously published means of treatment-seeking headache patients (41, 42).

Following assessment, subjects were placed on a restricted diet adapted from Theisler (43). (The diet is available from the corresponding author.) This diet restricts TYR, PEA, HIS, nitrites, caffeine, monosodium glutamate, and aspartame. Subjects recorded in a diary on a daily basis everything they ate. Headache activity ratings were also made four times a day on a 0 (no headache) to 10 (maximally severe headache) scale. These ratings were recorded in the same daily diaries. After completing a 2-week "wash out" period on the diet, subjects began the series of four provocative trials with chocolate or the carob placebo while remaining on the diet for the duration of the trial period. The trials were double-blind, and neither the subject nor the individual providing the sample was aware of whether the substance ingested was the chocolate or carob product. A Latin square design was used to control for order effects, and subjects were randomly assigned to any of the six possible presentation orders of the two carob trials and the two chocolate trials.

Food trials were scheduled during a non-menstrual week, with at least 3 days between each trial. Subjects were instructed not to come in for a sample if they already were experiencing a moderate headache with an intensity of at least 6 on the 0 to 10 scale. Food samples were given to each subject by a blinded staff member. Subjects were required to consume the entire sample in a single sitting in the clinic and to return the empty wrappers to the experimenter before leaving the clinic. They recorded the time of consuming the sample in their diaries.

Results

Chocolate/carob analysis

Both the chocolate and carob bars were analyzed for bioamine as well as caffeine and theobromine content. Results of this testing and a comparison with previously reported amine levels in chocolate are presented in Table 1. The chocolate sample results reveal a chemical profile similar to previously published analyses of commercial chocolate products. This analysis demonstrates that the chocolate sample used in this study was chemically similar to a commercially sold chocolate bar.

Subject characteristics

Eighty-one women were evaluated for the double-bind portion of the study. A total of 18 women dropped out of the study, 14 of whom (77.8%) dropped out before starting the food trials. Most dropouts cited the difficulty of staying on the diet or time constraints as the reason for terminating participation in the study. The four women who dropped out of the study after initiating the food trials did not offer reasons and did not return telephone calls to inquire about why they had dropped out. Three of these women had completed one trial and returned diaries from the day after the trial, and these three trials were included in the analyses. None of the three had reported more than a mild headache after eating the sample, thus the perception of sample-induced headache was ruled out as a possible reason for cropping out of the study. Sixty-three women competed the study, with a mean age of 28.3 years (SD = 10.7). Other demographic and headache characteristic information is presented in Table 2.

The mean scores on the psychological questionnaires were compared with previously published means for migraine patients, and are presented in Table 3. The current study sample reported significantly less headache pain and life interference due to pain, but was otherwise comparable to a treatment-seeking patient sample.

Eleven subjects (17.5% of the sample) reported that chocolate was a trigger for their headaches. Seven of the 11 were migraine patients, two were tension-type headache sufferers, and two were combined headache sufferers. For the entire sample, the most commonly cited trigger for headache was stress (87.6%), followed by a change in sleep patterns (76.8%), menstruation (64.6%), and hunger (61.0%). These percentages are also comparable to the reports of treatment-seeking headache samples (13).

Table 1. Chemical analysis of chocolate and carob samples.

	Chocolate sample	Chocolate in the literature	Carob sample	Carob in the literature
Phenylethylamine (mg/g)	1.91	0.4–6.6[a]	0.39	not available
Theobromine (mg/g)	2.4	0.38–6.4[a] average 2[c] 1.36–5.65[d]	0.0007	0[d]
Caffeine (mg/g)	0	average 0.2[c] 0.116–0.617[d]	0	0[d]
Tyramine (μg/g)	0	3.8 12[d]	0	
Spermine (μg/g)	1.63	not available	not available	0

[a] Hurst WJ, Toomey PB. High-performance liquid chromatographic determination of four biogenic amines in chocolate. Analyst 1981 ;106:394–402.

[b] Schweitzer JW, Friedhoff AJ Schwartz R. Chocolate B-phenylethylamine and migraine re-examined. Nature 1975;257:256–7.

[c] Shively CA, Tarka SM. Methylxanthine composition anti consumption patterns of cocoa and chocolate products. In: Spiller G, editor. The methylxanthine beverages and foods: chemistry consumption and health effects. New York: Alan R. Liss, Inc., 1984, 149–78.

[d] Craig WJ, Nguyen TT. Caffeine and theobromine level in cocoa and carob products. J Food Sci 1984;49:302–5.

Table 2. Demographics and characteristics of the study sample (n = 63).

Mean age = 28.3 years (SD = 10.7)
Range = 18 to 64

Mean years suffering from headaches = 10.2 (SD = 9.1)

Employment status:	
Working full or part time	65.0%
Unemployed	9.5%
Homemaker	7.9%
Student	17.6%

Education level:	
Some high school	3.1%
High school degree	12.5%
Some college	39.1%
College degree	26.6%
Graduate school experience	18.7%

Ethnic background	
Caucasian	78.1%
African American	10.9%
Asian	9.4%
Other	1.6%

Diagnosis:	
Migraine[a]	50.0%
Tension-type headache	37.5%
Combined migraine and tension-type headache	12.5%

[a]Includes both migraine with and without aura.

Table 3. Questionnaire scores.

Questionnaire	Mean score of sample[1]	Mean score of comparison sample[2]
Multidimensional Pain Inventory:		
Pain severity scale	2.1 (1.1)	3.1 (1.1)
Life interference scale	1.4 (1.1)	3.1 (1.2)
Life control scale	3.8 (1.0)	3.5 (1.0)
Affective distress scale	2.9 (1.3)	2.7 (1.2)
General activity	3.0 (0.8)	3.0 (0.7)
Headache locus of control scales:		
Internal locus of control	36.9 (7.3)	33.2 (9.3)
External locus of control	24.6 (8.2)	28.3 (7.8)
Chance locus of control	27.8 (8.5)	33.3 (8.2)
Center for Epidemiological Studies Depression Scale	14.3 (9.4)	14.2 (10.5)[3]

1 Standard deviations are indicated in parentheses.

2 Mean scores for 129 treatment-seeking migraine patients published in Scharff L, Turk DC, Marcus DA. The relationship of locus of control and psychosocial-behavioral response in chronic headache. Headache 1995;35:527–33.

3 CES-D scores from sample of 132 treatment-seeking migraine patients previously published in Scharff L, Turk DC, Marcus DA. Psychosocial and behavioral characteristics in chronic headache patients: support for a continuum and dual-diagnostic approach. Cephalalgia 1995;15:216–23.

Chocolate/carob taste ratings

At the time of the food trials, subjects were asked to make their best guess as to whether they were or were not eating chocolate. A total of 260 taste test questionnaires had been completed. A kappa statistic was calculated comparing subjects' guesses to what they actually ate, and was not significant (k = 0.06, p = 0.32).

Diet compliance

Compliance with the dietary restrictions was monitored throughout each subject's involvement in the study. Subjects recorded what they ate on a daily basis, and all deviations from the dietary restrictions were counted as such, regardless of the amount of prohibited food that was consumed. Special attention was paid to days in which test samples were consumed. Of the 245 sample days that were included in the analysis, 119 (49.2%,) were deviation-free. Ninety-five percent of the time subjects recorded three or fewer deviations on the day of the sample. The most frequently listed diet deviations were prepared foods containing MSG (e.g., canned soups) or cheese. A chi-square comparison of diet compliance on sample days and a headache occurring on a sample day was not significant (${}^{2}(1) = 0,001$, p = 0.99), indicating that diet compliance did not significantly influence headache occurrence on a sample day.

Headache analyses

Overall sample. A total of 245 food trials were included in the analysis. information from 10 samples was not included because insufficient headache information was provided by the subject (*n* = 9), or because the subject recorded a moderate to severe headache before eating the sample (*n* =1).

The first analysis was a chi-square comparing incidence of headache within 12 h following ingestion of the sample to the type of sample consumed. The data for this comparison are presented in Table 4. No significant differences were obtained (^{2}(1)=0.17, *p*<0.68). Subjects were equally likely to report headaches after eating the chocolate or the carob.

A total of 32 women (51% of the sample) did not report a headache on any occasion after eating either sample. Three women reported a headache after both chocolate samples and not after either of the carob samples, and three women also reported a headache after both carob samples and not after either of the chocolate samples. Six women consistently reported a headache after all four samples.

When a subject did report a headache, she was asked to record what she perceived to be the trigger of the headache. The most frequent answer was that there were multiple triggers (31%), followed by stress (16.9%). Fourteen percent of the time, women did not on could not identify a trigger for their headaches. Only on three occasions (3.1% of the time) was chocolate indicated as the sole trigger of the headache, and only on one of those three occasions had the subject actually eaten chocolate.

Table 4. Report of headache within 12 h of eating sample.

		Headache	
		No	Yes
Entire sample	Chocolate	53 (82.8%)	11 (17.2%)
	Carob	38 (59.4%)	26 (40.6%)
Subjects who thought chocolate is a trigger	Chocolate	9 (81.8%)	2 (18.21%)
	Carob	7 (63.6%)	4 (36.4%)
Headache before, eating sample (total number of trials)	No	144	51
	Yes	9	41

Subjects identifying chocolate as a trigger

The chi-square analysis was also repeated using only the trials of the 11 women who believed chocolate was a trigger for their headaches (a total of 41 trials were included in this analysis, as three trials contained insufficient information). This information is also provided in Table 4. Again, the findings were not significant (X^2(1)=0.73, *p*=0.39). Even in women who believed chocolate was a trigger for their headaches, headaches were equally likely to occur following ingestion of either the carob or chocolate.

Influence of mild headache prior to eating sample

On 50 occasions (20.4% of the time), subjects reported a mild headache before eating their samples. An additional analysis was performed to identify whether or not having a mild headache before eating the sample had an effect on report of headache after earing the sample. These data are presented in Table 4 in terms of the total number of samples, and the chi-square calculation was highly statistically significant ($X^2(1)=52.9$, $p<0.001$). The results demonstrate theft if subjects reported no headache prior to eating the sample, they were likely to report no headache afterwards, and subjects who already reported the presence of a mild headache before eating the sample were significantly more likely to report continuing to have a headache afterwards. Paired t-tests comparing headache intensity ratings before eating the sample to the highest rating up to 12 h after eating the sample showed that headaches were likely to grew in intensity after eating either the chocolate

($t(123)=3.08$, $p<0.003$) or the carob ($t(120)=5.16$, $p<0.001$) samples. Thus, headache intensity was not more likely to increase after eating chocolate than after eating carob.

Influence of headache diagnosis

Presumably, chocolate should be a stronger trigger of headache in women with a diagnosis of migraine, in contrast to tension-type headache -PEA is proposed to trigger headaches mainly through its vascular effect, and migraine is proposed to have a stronger vascular component than tension-type headache. A comparison of headache activity for each diagnostic category after eating the chocolate and carob samples was conducted to investigate the potential differential effect of chocolate for each type of headache. Only cases where subjects reported complete absence of headache were used. The results are presented in Table 5. There were no differences among headache diagnostic groups in whether a headache occurred after eating chocolate ($^2(2)=0.36$, $p=0.83$), or carob ($^2(2)=1.86$, $p=0.39$).

Conclusions

The results of this study suggest that chocolate does not induce headaches in a general sample of headache sufferers. The recipe used to manufacture the chocolate and carob samples in this study was dentical to that used in the Gibb study (1), where the chocolate sample was related to the occurrence of headache in 42% of the sample, and carob falled to trigger headache. Chemicals demonstrated or postulated to trigger migraine were identified in the chocolate sample, whereas their presence in the carob sample was minimal. The concentration of phenyl-ethylamine and theobromine found in our sample was similar to levels found in commercially available candy bars (35, 44).

Our findings are in contrast to previous studies that have suggested chocolate is a headache trigger (e.g., 1, 9). There are several methodological differences that may explain this discrepancy. First, the present study was designed such that exposure to other headache-triggering foods was restricted. Previous studies did not report such dietary restrictions. It is possible that ingestion of other vasoactive amine containing foods acts as a "primer" for other headache triggers. In other words, although chocolate alone may be inadequate to trigger headaches, when combined with other headache food triggers, such as colas, pizza, or peanut butter, there may be synergy with the combination providing an adequate rigger. This study, however, did not demonstrate that failure to adhere to the diet on testing days increased the likelihood of a headache.

Table 5. Headaches after eating sample by diagnostic category.

		Headache after eating chocolate (n=96)	
		NO	YES
	Migraine, with or without aura	76.9%	23.1%
IHS Diagnosis	Tension-type	71.8%	28.2%
	Combined migraine and tension type	77.3%	22.7%
		Headache after eating carob (n=99)	
		NO	YES
	Migraine, with or without aura	66.7%	33.3%
IHS Diagnosis	Tension-type	67.4%	32.6%
	Combined migraine and tension-type	79.5%	20.5%

Secondly, both the Hannington and Gibb studies utilized only migraine sufferers who specifically identified chocolate as a trigger of their headaches, and who in addition had eliminated chocolate from their diets because of this. Hannington (30) has reported that only 5%. of headache sufferers met this self-imposed diet restriction criterion. Therefore, a very select group of headache sufferers was involved in these studies. The current study was designed to investigate the incidence of chocolate-triggered headache in a general sample of headache sufferers, and we did not utilize the same screening criterion. It is possible that our findings were negative simply because we used a general headache-suffering group, not individuals who had identified chocolate as a trigger. The number of headache sufferers included in our study who did identify chocolate as a significant trigger of headaches (n=11) was similar to the entire sample size of previous chocolate challenge studies, and 7 of those 11 women suffered from migraine.

Finally, the current study was conducted with a much larger sample size than previous headache diet challenge studies, and each subject was exposed to two trials of both the chocolate and carob samples. Our results demonstrate that chocolate may not be a trigger for the general headache-suffering population, and the way in which we conducted the study ensures that we had adequate power to detect chocolate-triggered headaches. Hannington and colleagues have suggested that 5% of migraine sufferers have chocolate-triggered headaches, and three women in our study (4.7%) did report headaches after chocolate and not after carob. However, the same number of women also reported headaches after carob and not after chocolate.

The only factor that seemed to influence the development of a headache after eating the sample was the existence of a mild headache prior to eating the sample. These headaches appeared to worsen throughout the following hours regardless of what the subject ate. The incidence of headache in our sample may seem relatively high because we allowed individuals with mild headaches to participate in eating the samples. Our inclusion of tension-type headache sufferers who often experience constant or very frequent mild headaches required that we allow some of our subjects to have headaches at the time of ingestion.

Interestingly, although chocolate is frequently identified as a headache trigger by medical texts and patients, our results do not support this association. Patients' experiences with sweet/chocolate cravings may lead to an erroneous assumption of a causal relationship between chocolate and headache. Sweet craving has been identified as a prodrome to the onset of headache (45). Fulfilling this craving with chocolate could then lead to the belief that the chocolate caused the headache. In addition, in about 60% of women, headache is related to menses. Premenstrual sweet craving may cause patients to associate the chocolate with menstrual headaches, Finally, stress is identified as a headache trigger for the majority of chronic headache sufferers. Stress has also been linked to sweet cravings, permitting the sweet, rather than the original stress to be identified as the headache trigger.

There are several limitations to our study that restrict the interpretation of the results. Primarily, the subjects included in this study were volunteers who represent a headache-suffering population in general, not a clinical population of treatment-seeking headache sufferers. The sample of women who participated tended to be younger than the typical headache patient, and reported significantly less pain and life interference associated with headache in comparison to treatment seekers. Our inclusion of exclusively female volunteers also limits the generalizability of our findings to one gender. Finally, there was a significant amount of non-compliance with the restrictive diet. Although we found no differences in headache incidence between subjects who fully complied with the diet and those that did not, we cannot truly report that chocolate was ingested on all occasions in isolation of other vasoactive amines.

Although vast biochemical literature theorizes an important role of a variety of chemicals contained in foods for triggering headache, and anecdotal reports support these associations, further research should focus on prospective trials of additional dietary elements to determine the true role of diet in headache. Research will need to determine whether diet is a trigger for headache for a general headache population, for a select sample of the population, or not an important headache trigger.

Acknowledgements .— This research was supported by grants from the Raymond and Elizabeth Bloch Educational and Charitable Foundation and the American

Cocoa Research Institute.

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