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Highlights of the recent national diet-heart study

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THE serious question of whether diet is or is not an important factor in producing atherosclerosis with its associated coronary and cerebral disease has not yet been tested. In the spring of 1960, a group of scientists met to explore ways and means for conducting such a test. As a result of these deliberations, The National Diet-Heart Study was undertaken.

Experience in the conduct of a large-scale study had to be acquired before such an experiment to demonstrate an association between diet and heart disease could be undertaken. The proposed diets increased polyunsaturated fatty acids and decreased saturated ones as well as cholesterol itself. The free-living participants of the study required accustomed food products easily available, a requirement necessitating specially processed foods to implement dietary changes. Patterns of eating were emphasized because the word 'diet' suggests to lay persons something highly restrictive and often distasteful. It was uncertain whether or not the confirmed eating habits and pleasures of most persons could be changed, even with their consent.

Consequently, it was the purpose of the two-year Feasibility Trials of The National Diet-Heart (D-H) Study to develop technics for testing the hypothesis that diet ultimately is important in preventing coronary heart disease by lowering the cholesterol content of the blood. This paper presents highlights of the recent report[1] of the study.

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CONDUCT OF THE EXPERIMENT

Selection of participants. Diet-Heart Centers* were established in five cities and in a state hospital. A uniform program of nutritional and clinical procedures was coordinated by a central staff.†

Participants were chosen in the following fashion. Names of the men who satisfied study qualifications were selected from census tracts in four cities, and from insurance lists in one city. Letters were mailed by the Census Bureau and insurance companies. Recruits were free from metabolic and organic disease as determined by physical examination and a medical history. Their living habits allowed them to meet the nutritional and program requirements. Age and medical requirements had to be liberalized to obtain sufficient institutional subjects. Approximately 2000 healthy, free-living men, from 45 to 54 years old, and 400 inmates of the mental hospital, from 40 to 59 years old, partook in the Feasibility Trials, which lasted two years. During the month or more of the base line period, each volunteer visited a center three or four times, so that a blood sample could be taken for determination of serum cholesterol, and body weight and blood pressure noted. Food intake was recorded at meal times by the volunteer for seven days during this base line period to obtain information on the habitual nutrient intake. A four-week "mixed-diet" period, in which a mixture of the three varieties of D-H foods was supplied to the participants, was introduced to eliminate the irresolute participant. Then 75 participants were randomly assigned by the statisticans to each diet group at each center, and were equally distributed according to their base line serum cholesterol levels, blood pressures, relative body weights, and status in regard to cigarette smoking.

Diets. The experimental diets used in the study were based on the experience of committee members. Of the three principal diets, one was low

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Boston, Mass.	Fred Stare, M.D.	Robert McGandy, M.D.	Patricia Remmell, M.A.
Chicago, Ill.	Jeremiah Stamler, M.D.	Louise Mojonnier, Ph.D.	Yolanda F. Hall, B.S.
Faribault, Minn.	Ivan D. Frantz, Jr., M.D.	Ancel Keys, Ph.D.	Patricia Ashman, B.S.
Oakland, Calif.	Laurance Kinsell, M.D.	S. Splitter, M.D.	Barbara Gunning, Ph.D.
Twin Cities, Minn.	Ancel Keys, Ph.D.	E. S. Fetcher, Ph.D.	Nedra Foster, B.S.

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Table 1.—*Fat composition of diets as reported during base line and experimental periods, first study*

Center	Diets*	Calories	Total fat, calories, %	Saturated fatty acids, calories, %	Polyunsaturated fatty acids, calories, %	Cholesterol, mg/day	P/S†
Urban	Base line	2560	40	16	4	535	0.2
Hospital		2300	37	17	5	297	0.3
	B. Specified		30	7	11	350	1.5
Urban		2150	30	7	10	280	1.4
Hospital		2550	29	6	12	226	2.0
	C. Specified		40	9	18	350	2.0
Urban		2260	34	7	13	290	1.8
Hospital		2600	38	7	18	234	2.5
	D. Specified		40	14	6	650	0.4
Urban		2230	35	12	5	325	0.4
Hospital		2600	40	16	5	257	0.3

* Coding is arbitrary lettering.

† Ratio of polyunsaturated to saturated fatty acids.

in fat, one contained polyunsaturated fat, and the control diet had saturated fat (*Table 1*). Diets were administered on a double-blind basis. In the state hospital, foods were planned and prepared in a central kitchen by a nutritionist and her staff according to diet specifications; participants and the investigator were not told the specific diet assignments and serum cholesterol levels. In the urban centers, participants, investigators, and nutritionists did not know the diet assignments or serum cholesterol levels. All participants were instructed in a single diet plan; differences in nutrients among the three diets were maintained with special D-H foods available through local D-H food centers. Only the food managers at the local centers knew the diet assignments. They filled individual orders with the appropriate variety of D-H foods.

The diet plan indicated the number of servings to be selected from each of five categories of products that were similar in fat and nutrient content. *Category 1* consisted of lean meats, fish, poultry, and eggs; *category 2,* of low-fat, high-carbohydrate products, including starchy vegetables, cereals, breads, and sweets. *Category 3* comprised food products in which the fat content could be modified; these included meat such as hamburger and frankfurters, dairy products, rich baked goods, and miscellaneous products. *Category 4* consisted of fruits and vegetables, all low in fat; *category 5,* fats and oil including margarine, shortening, and salad dressings.

D-H foods consisted of lean meats (category 1), fat-modified foods (category 3) and visible fats (category 5). Except for lean meat, three varieties of each food product which differed in fat content were available. Foods for the control diet were made with saturated fat; those for the other two experimental diets were made with unsaturated oil; products for the low-fat diet had less oil than those for the higher fat diet.

A subgroup of participants was on a diet similar to the low-fat diet; they did not use D-H foods but obtained all foods from the market. An unmanipulated control group was not given a diet, but food intake, body weight, and serum cholesterol values were recorded. A highly unsaturated fat diet was also used in the state hospital. It was too restrictive to be practical for use in urban centers.

The second year, diets and dietary programs were modified and tested in subgroups of participants. New volunteers were recruited along with participants from the first year. The low-fat and unsaturated diets were merged into one diet by utilizing the most acceptable food products from both diets. A more unsaturated fat diet than the diets used the year before, with a specified ratio of polyunsaturated to saturated fatty acid content (P/S) of 3.0, and a more saturated fat diet—specified P/S = 1.0—were used. Some participants selected lean meat from the regular markets instead of buying the expensive D-H meats. A flexible diet plan was instituted in which D-H foods were chosen, with only meat and eggs restricted.

During the experimental diet period, body weight and blood pressure were recorded and blood samples taken for serum cholesterol determinations at intervals of from 4 to 8 weeks. Seven-day food records were made three times a year by free-living participants and were the bases for estimates of nutrient intake. Dietary adherence was estimated subjectively by the nutritionists at each consultation and also from information in regard to foods eaten during the previous week. In an attempt to obtain an objective measure of adherence to diet, the fatty acid composition of erythrocytes was determined of every participant once or twice during the base line period, three times during the first year, and twice during the second year. Serum triglyceride levels, fatty acid composition of serum cholesterol esters and of adipose tissue were also determined on subgroups of participants.

Chemical methods. Serum cholesterol was determined by a modified, semiautomated Abell-Kendall method at the Lipid Standardization Laboratory of the Communicable Disease Center, United States Public Health Service. Fatty acid composition of the tissues was analyzed in three laboratories associated with the D-H study, in Oakland, California, in Twin Cities, Minnesota, and in Boston, Massachusetts, by gas liquid chromatography. Triglycerides were determined in the laboratories in Oakland and in Twin Cities. Diet-Heart foods were analyzed by the Woodson-Tenent

Laboratories for water, total fat, protein, ash, cholesterol, and fatty acid distribution. Details are given in the full published report.[1]

RESULTS

Recruitment. Ten percent of the men to whom invitational letters were sent volunteered for the study the first year, and 5 percent the second year (*Table 2*). The season of the year and the amount of publicity and enthusiasm of the orientation meetings were factors affecting the number of volunteers. Enthusiasm remained high when persons were inducted into the study soon after they volunteered; it waned when a considerable time elapsed before induction.

Participants. The method of assigning participants to the diet not only equalized the groups in regard to serum cholesterol levels, blood pressures, relative weights, and cigarette smoking, but also in regard to race, nativity, education, occupation, and nutrient composition of their respective usual diets. Participants were more highly educated, had higher incomes, and more were professionally employed than the average man in their census tracts. Only one third of the participants smoked cigarettes, compared with more than half of the men in the general population. Weights of participants were similar to those of other American men of the same ages.

Exclusions and dropouts. Of the 2000 persons screened the first year, one third did not meet medical or program requirements (*Table 3*). Medical exclusions were based on the evidence of abnormality on electrocardiograms (34 percent of medical exclusions) and on roentgenograms, overweight of more than 1.4 times ideal weight (24.8 percent), angina pectoris or a history of myocardial infarction (12.4 percent), and peptic ulcer. Only 15 persons (0.75 percent) were excluded because of serum cholesterol content of more than 350 mg per 100 ml. Nutritional exclusions were made because of frequent meals eaten away from home or because of special therapeutic diets. Five percent of participants withdrew from the study during the base line period, and 6 percent more during the mixed-diet period.

Table 2.—*Recruitment from census tracts and insurance lists*

Item	January, 1963	June, 1964
Total mailings, number	38,704	19,942
Delivered mailings, percent	93.5	81.4
Number of men at orientation meetings, percentage of delivered mailings	15.9	6.9
Volunteers,		
Percentage of delivered mailings	11.1	5.5
Percentage of total mailings	10.4	4.5

Table 3.—*Exclusions, withdrawals, and dropouts, first and extended studies*

Period	Number of persons	
	Total	Exclusions, withdrawals, and dropouts
Base line	1988*	685 (403†, 178‡)
Mixed diet	1295*	84
Experimental diet	1211*	136
End, first year	1075	—
Reenlisted—second year	624*	71
End, second year	553	—

* In program at beginning of period.
† Medically excluded.
‡ Nutritionally excluded.

Subsequent withdrawals during the experimental period amounted to 8 percent of the original volunteers, many of whom left during the first three months. The two most frequent reasons given for leaving the study were the inability to meet study appointments because of travel commitments, and an uncooperative wife. Men who left the study weighed more and smoked more than those who remained active in the study, and the former had a 5.5 percent average less reduction of serum cholesterol content. There were few exclusions during the study. Of the 51 exclusions, 34 were due to noncardiovascular disease, the majority because of peptic ulcers. The dropout rate was the same for those in all diet groups. The first year, an overall loss of one half the volunteers originally screened was sustained for all reasons (*Table 3*).

All participants completing the first year were asked to volunteer for a second year; 41 percent did not return. Reasons for refusing included interference with business and social life, quality of D-H foods, lack of cooperation of the wife, and rigidity and complexity of the diet program.

Diets. The base line diets, the two experimental, and the control diets contained adequate nutrients, vitamins, and minerals, which more than met the requirements of the National Research Council.[2] Protein was from 15 to 16 percent of calories in base line diets, and from 17 to 18 percent in the other diets. There was no deficiency of vitamin E in the polyunsaturated experimental diets, according to the serum tocopherol concentration in a subgroup of participants.

The nutrients of the base line diet were similar to those of the customary American diet.[3] The diet contained 2,500 calories, 40 percent of which was fat (*Table 1*), and was the same for all centers despite regional differences in food usage. For example, more dairy products were consumed in Boston, more butter and margarine in the Twin Cities, and more salad

oils in Oakland than in each of the other cities. Foods habitually served at the state hospital provided less fat and cholesterol than those eaten by free-living people.

Specifications of the experimental diets were not met in all cases. The control diet did not have sufficient cholesterol as prepared in the state hospital, although all other requirements were met. In urban centers, specifications were met for the low-fat diet; total fat and polyunsaturated fatty acids were low in the unsaturated diet; total fat, and saturated fatty acids and cholesterol were less than specified for the control diet. In addition, experimental diets were consistently 300 calories less than the base line diets because of decreased fat content. The fat compositions of the two experimental diets were more alike than planned, so that for the second year the best D-H foods used in both diets were combined to make one modified diet.

Foods. By themselves, D-H foods when selected according to diet plans would have fulfilled diet specifications except for cholesterol. These foods consisted of the staple fat-containing products most frequently used in meals. They were palatable and acceptable. The three varieties of each kind of product were sufficiently alike to maintain the double-blind requirement. There were no differences in dropout rates among participants in the three diet groups.

Production of the D-H food products proved to be feasible, in general. Lean meat cuts, hand-trimmed of fat by the processor, were expensive. Lean cuts bought by the cook from the open market and trimmed in the kitchen were substituted successfully for D-H meats the second year. The relatively small amount of any one product required for the study was a handicap in the commercial production of some products. For instance, the number of mince pies produced in a single batch was much more than could be used at the six centers during the winter holiday season. For this reason it was impossible to provide seasonal and less frequently used food items that give variety and interest to the menu. In some instances, the most palatable product suitable for one diet could not be used because it did not match in flavor or appearance its counterparts in the other two diets.

The double-blind basis for administering the diets was carried out successfully. Answers to questionnaires filled out at the end of the first year indicated that participants were unable to guess the fat content of their diets and that study personnel were likewise unable to guess diet assignments. This was the first nutritional study of its kind to use a double-blind design.

Adherence. One fourth of the free-living participants adhered excellently to the diets, one fourth, poorly. These proportions held whether adherence was measured subjectively by the nutritionists, or by an estimate of food intake, or by fatty acid content of any of the three types of tissue analyzed. For the Oakland centers, where three types of tissue in the same subjects

Table 4.—*Mean changes in tissue linoleic to oleic acid ratios (L/O), and in serum cholesterol levels in individuals according to subjective adherence ratings; Oakland D-H center, unsaturated fat diet, 44 weeks*

Tissue analyzed	Total, 74 men	Excellent, 20 men	Good, 8 men	Fair, 30 men	Poor, 16 men
			Percentage change		
Erythrocytes	+14	+32	+12	+5	+8
Adipose	+71	+85	+59	+76	+51
Serum					
Cholesterol esters	+68	+89	+81	+61	+49
Cholesterol	−11.5	−15.7	−10.8	−11.4	−6.7

were analyzed, the ratio of linoleic to oleic acid (L/O) in adipose tissue increased, from 0.27 with the base line diet, to 0.47 with the diet highest in linoleic acid. The L/O ratio in erythrocytes increased from 0.69 to 1.00, and that of the cholesterol esters from 2.65 to 4.64. The nutritionists' subjective estimates corresponded best with serum cholesterol changes (*Table 4*).

Adherence was excellent for all state hospital participants because of the well-controlled food preparation, food service, and high attendance at meals (96 percent). Here there was little subversion of the diets through restaurant meals or additional foods high in saturated fat. Adherence is discussed further in connection with serum cholesterol changes.

Serum triglyceride levels. As an ancillary study, serum triglyceride concentrations were determined at the Oakland and the Twin Cities laboratories for participants in Oakland, Twin Cities, and the state hospital. There was a variation between centers which was hard to interpret, though it is clear that the main effect of the diets was to lessen serum triglyceride content, particularly in men with initially elevated base line levels.

Serum cholesterol levels. Control levels of serum cholesterol measured during the base line period were similar to those in the general population, and confirmed prior observations that persons in institutions have levels lower than those of free-living people. In 962 urban men who completed the first year, the average base line serum cholesterol content was 230 mg per 100 ml ± 39 mg SD.* In 192 men in the hospital, the average serum cholesterol content was 207 mg per 100 ml ± 40 mg SD. In an individual, the average difference in three base line blood samples was ±12 mg per 100 ml.

There were only small differences among the various experimental diets in their effect on serum cholesterol. The low-fat and unsaturated-fat diets

* *SD = standard deviation.*

Table 5.—*Average decreases in serum cholesterol content for the entire experimental period*

Diet description	Free-living centers base line level, %	Institutional center base line level, %
Principal diets		
Low fat	12	17
Unsaturated fat	13	15
Control, saturated fat	3	3
Food source differences		
Combined low fat and unsaturated fat		
D-H meats	11	17
Store meats	11	16
Low-fat store foods	12	—
Open control store foods	0	—
Diet plan differences		
Combined low-fat and unsaturated fat		
Structured	11	—
Not structured	10	—

reduced serum cholesterol levels by 12 to 13 percent in urban participants and by 15 to 17 percent in institutional participants (*Table 5*). The two experimental diets used the second year had a similar effect. With the highly unsaturated fat diet used only in the state hospital, serum cholesterol was reduced 19 percent. With the control diet, serum cholesterol decreased 3 percent at all centers. There were no changes (from base line levels) in serum cholesterol values in the persons in the control group who were not given diets.

The extent of reduction of serum cholesterol content also reflected the degree of adherence to the diets. All institutional participants were considered to be excellent adherents. Participants in the cities were rated subjectively by the nutritionists in four categories from excellent to poor. The combined effects of the low-fat and unsaturated-fat diets on serum cholesterol reduction were graded according to adherence ratings. Free-living participants with an excellent rating had a decrease in serum cholesterol content within 3 percent of that obtained in the institution. This difference between reduction in the institutional and free-living participants became increasingly larger as the degree of adherence worsened. In the same way, lack of reduction of serum cholesterol content correlated well with the number of restaurant meals eaten in a week.

The extent of decrease in serum cholesterol content also offers a measure of comparison between the various methods of administering the diets. Food products selected by participants in the regular markets were as effective as D-H foods. However the disadvantage in using market foods was

the extra time and effort required of nutritionists and participants for proper instruction in food choices. Decrease in serum cholesterol content in other subgroups showed that lean meats selected and prepared by individual housewives, or bought and prepared in the state hospital kitchen, were comparable to D-H lean meats in the effect on serum cholesterol. The flexible diet plan using D-H foods was also as effective as the rigid plan (*Table 5*).

Various factors other than diet are known to affect serum cholesterol levels. Of these, the season of the year had little if any influence. The base line serum cholesterol level influenced the extent of reduction; those levels higher than 240 mg per 100 ml, decreased from 20 to 32 mg more than did those with base line levels less than 210 mg. As is well known, weight loss in itself causes a decrease in serum cholesterol content. Participants in urban centers lost an average of 6 lb. during the first 12 weeks with the experimental diets; they then regained 2 lb. slowly during the subsequent weeks (*Fig. 1*). This weight loss was reflected in the decrease in serum cholesterol content in free-living participants, with all diets, during the first few weeks of the experimental period (*Fig. 2*). The difference in serum cholesterol

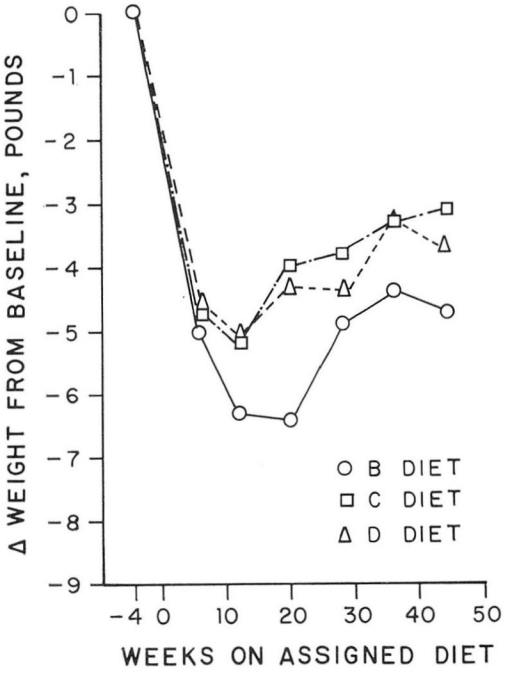

Fig. 1. Graph showing changes in weight during the first year in urban centers. (From National Diet-Heart Study Research Group: The National Diet-Heart Study final report, *Circulation* (suppl. I) **37:** I-1 – I–428, March 1968; and by permission of the American Heart Association, Inc.)

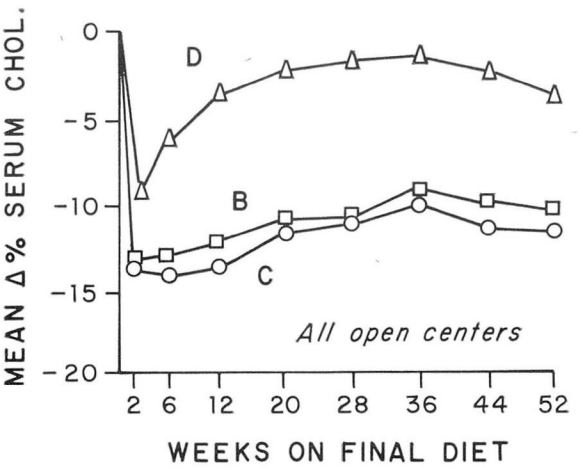

Fig. 2. Graph showing mean percentage changes in serum cholesterol content during the first year in urban centers. (From National Diet-Heart Study Research Group: The National Diet-Heart Study final report, *Circulation* (suppl. I) **37:** I-1 – I-428, March 1968; and by permission of the American Heart Association, Inc.)

levels between those losing more than 6 lb. and less than 2 lb. was 6 percent; that is, 15 percent and 9 percent reduction in serum cholesterol content, respectively, for free-living participants, and 20 percent and 14 percent for those in the institution.

Risk factors. Although only diets were deliberately altered, other conditions that are associated with the risk of heart disease changed at the same time. Not only serum cholesterol content was reduced as expected, but blood pressure dropped by 4 percent in the free-living participants, and by 12 percent in the hospitalized men. One half of those who at the beginning of the study habitually smoked cigarettes, reported that at the end they were smoking fewer cigarettes, and, of these, half had stopped smoking entirely. Because of the short duration of the study, nothing could be inferred about the direct effect of diet on the incidence of heart disease. There were 11 myocardial infarctions in all, a rate of 0.5 per 100 participants per year. (One infarction per 100 persons per year occurs in the general population.) Nine heart attacks occurred in persons with two or three risk factors that were above the median level for the group; i.e., blood cholesterol content more than 233 mg per 100 ml, relative weight more than 1.17 times above ideal weight, blood pressure higher than 84 mm Hg diastolic, and who also were smokers.

COMMENTS AND CONCLUSIONS

At the conclusion of the two-year Feasibility Study, the investigators recommended to the National Advisory Heart Council that a large-scale

study on the prevention of coronary heart disease by means of diet be planned and begun as soon as possible. This recommendation was based on the conclusion that the design of the study was successful and that the experience gained provides a firm basis for its operation. It was established that even though geographic distribution, physical plant, staffing, management, and timing of participant induction differed among the five centers, the effects of these variables were negligible and did not influence the results of the study. Concomitant studies in a state hospital were important because they were conducted advantageously on a double-blind basis and insured good dietary control. They also provided a standard for comparing results of studies of a free-living population.

The number of participants required for the proposed study was estimated as being approximately 60,000 men. This number of free-living volunteers could be obtained from 20 large cities that have in all more than 6 million men from 40 to 59 years old. The estimate is based on the assumption that a 10 percent decrease in serum cholesterol content is achieved with diet, and that a coronary heart disease rate of 10 per thousand persons per year is observed in the control population period.

The double-blind program was not included in the recommendations because the disadvantages outweighed the advantages in the two-year study.[4] Motivation of participants was difficult to effect under the double-blind requirement. There were no tangible goals for nutritionists or participants because diet composition and serum cholesterol levels were not known to them. Dietary specifications were not entirely fulfilled, formulation of food products was hampered, food preparation in the home was hindered, and an estimate of adherence (other than a subjective impression) was difficult.

The significance of the results of a large study could be seriously impaired as a consequence of poor adherence. The number of poor and fair adherents (44 percent in the recent study) could be reduced by strengthening the motivation of the participant and of his wife, by removing some dietary restrictions and offering a greater variety of foods.

The diets used in the Feasibility Study are suitable for a mass field trial. Serum cholesterol levels can be decreased more than 15 percent by these diets when foods are properly prepared according to the diet specifications.

Physicians and public health administrators are challenged by the extremely high incidence and mortality of coronary heart disease. Preventive measures are imperative. Recent reports on the close association between dietary change (and serum cholesterol reduction) and the occurrence of coronary heart disease are encouraging. But these reports concern relatively small numbers of men and do not solve the medical and public health problem. Consequently, the large study designed to give a definitive answer to the problem should be conducted soon.

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