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THE EFFECTS OF PROTEIN DIET ON INFECTIVE HEPATITIS

BY

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The effects of diet on the course of various forms of jaundice have been the subject of some controversy. The purpose of this paper is to report on a series of 61 cases of infective hepatitis in men, 32 of which were treated with a high-protein diet with superadded vitamin B complex, and 29 by a classical low-fat diet in which the protein was not augmented.

Definition of Cases

Past experience of infective hepatitis has made it clear that the severity and the duration of the disease are extremely variable (Stocks, 1944; Higgins *et al.*, 1945). Recent claims have been made that the causal organism of infective hepatitis and N.A.B. and homologous serum jaundice are either similar or closely related. The fact that those diseases differ in their clinical course is best shown in Table I. The present series of 61 cases of infective hepatitis are compared with 54 cases of homologous serum jaundice resulting from the same icterogenic yellow fever vaccine. These have been arranged into four groups, depending upon the duration of the illness as originally suggested by Fox *et al.* (1942). The number of cases in each group has been expressed as a percentage of the total in each series.

TABLE I.—Comparison with Serum Jaundice due to Yellow Fever Vaccine

	Serum Y.F. Jaundice		Infective Hepatitis
	Fox <i>et al.</i>	Personal Series	
Days under treatment:	%	%	%
A: 21 or less	25	19	8
B: 22-49	40	39	86
C: 50-89	23	27	5
D: 89 or over and fatal cases	12	15	0
Cases in each series	759	54	61

It appears from the table that the majority of patients with infective hepatitis fall into Group B, whereas those of serum jaundice are spread over a longer period. This would suggest that the recovery rate of serum jaundice is of a scattered nature; in some the disease is transient, in others there is a greater tendency to relapse (10%). On the other hand, infective hepatitis appears to be largely self-limiting and recovery spontaneous.

In selecting cases for this experiment, therefore, the importance is stressed of using only those patients who gave a history of contact or in whom there was adequate epidemiological evidence of the disease. All cases which had been under arsenotherapy or had had yellow fever vaccine of an unknown batch number, or had had transfusions within 200 days of onset, were excluded. Five W.A.A.F. personnel were also treated under similar conditions, but, owing to paucity of numbers and possible sex differences in the rate of return to normal, these have not been included.

To exclude cases of Weil's disease a leucocyte count was made on entry, and in no case was a total of over 10,000 per c.mm. found. Infective mononucleosis was ruled out by differential counts and by the classical Paul-Bunnell reaction on

selected cases. Only those who contracted the disease between Nov., 1943, and May, 1944, have been included in this series.

Criteria of Progress

During the course of treatment to assess progress four criteria were observed. (These were all based on the time taken to return to normal after admission to hospital.)

The first—the presence daily of bile in the urine—was tested by the iodine and foam test. The second—the excess of bilirubin in the serum—was assessed by the quantitative van den Bergh reaction as described by Harrison (1937), using the Lovibond disk. Normal was taken as being less than 0.6 mg. per 100 c.cm.; this test was made every fifth day initially, but later was carried out when the clinical signs suggested the icterus was minimal. The third criterion was the degree of parenchymatous liver degeneration as determined by the intravenous hippuric acid test of Quick (1939). The analysis of the urine, however, was carried out by the method of Weichselbaum and Probstein (1939). Two-hourly samples were used throughout, as these were considered to be more exact and sensitive. The fourth criterion was the time taken to return to duty.

Conditions of Experiment

It was decided to try the effects of foodstuffs readily available, supplementing these with vitamin B complex in the form of bakers' yeast. Two diets were arranged; the first, based on those of Patek and Post (1941) and Fleming and Snell (1942), contained 370 g. carbohydrate, 154 g. proteins, and 108 g. fats. Vitamin B complex was given as bakers' yeast, 30 g. daily by mouth. Parenteral liver (2 c.cm. of anahaemin) and thiamine hydrochloride 5 mg. were given twice weekly subcutaneously. Later the original diet was modified to a more fluid character for some patients in the initial stages. The second was a classical low-fat diet—320 g. carbohydrate, 70-90 g. proteins, 60 g. fats—and acted purely as a control. Vitamins were not supplied in excess of those already contained in the diet. Table II gives details of the diets used in the investigation.

Through the courtesy of the commanding officer a 40-bed ward was set aside for the treatment of infective hepatitis. Cases were admitted alternately, without prejudice, to the right and left sides of the ward. Those on the left side received the high-protein and vitamin B diet, and those on the right the control. Officers were accommodated in the side wards and were given the same diets as the airmen. The ward was never completely filled at any one time, so that this method of random allocation to the diet group presented no difficulties.

While in hospital patients were kept in bed until their liver function was found to be normal by the intravenous hippuric acid method. When the urine became bile-free they were allowed to go to a convalescent home, or, in the case of officers, on sick leave. Initially, during the period at a convalescent home those on the high-protein diets were returned to their normal airman's rations (approximately 100 g. of protein a day), and yeast was withheld. Later, the high-protein diet and yeast were continued during the entire treatment. When in the opinion of the medical officer in charge of the

convalescent home evidence of clinical jaundice was minimal, the patient returned to the main hospital and the van den Bergh test was repeated.

TABLE II.—*Details of the Diets*

	Prescription (approximate)		
	High Protein (C., 370 g.; P., 154 g.; F., 108 g.)	Semi-fluid High Protein (C., 230 g.; P., 120 g.; F., 110 g.)	Low Fat (C., 320 g.; P., 70-90 g.; F., 60 g.)
Break-fast	90 g. prunes 30 g. cornflakes 15 g. sugar 180 g. milk 1 egg 60 g. bread 20 g. butter 15 g. sugar in tea 15 g. marmalade	180 g. milk 30 g. cornflakes 15 g. sugar 1 egg 60 g. bread 15 g. marmalade 20 g. butter	30 g. porridge 90 g. fruit 90 g. bread 90 g. marmalade 60 g. milk
9 a.m.	30 g. yeast 150 g. milk 15 g. sugar	30 g. yeast 150 g. milk 15 g. sugar	Lemonade 15 g. sugar
Dinner, 12 midday	90 g. meat 120 g. potatoes 90 g. vegetables 30 g. bread 20 g. butter 120 g. sweet 180 g. milk 15 g. sugar in coffee	90 g. mashed potatoes 15 g. butter 150 g. fish 90 g. vegetable purée 90 g. milk pudding	120 g. fish 120 g. potatoes 120 g. vegetables 90 g. milk pudding or fruit
2 p.m.	30 g. yeast 150 g. milk 15 g. sugar	30 g. yeast 150 g. milk 15 g. sugar	Lemonade 15 g. sugar
Tea, 4 p.m.	60 g. bread 15 g. butter 15 g. jam Green salad	60 g. bread 20 g. butter 15 g. jam	90 g. bread 60 g. jam 60 g. milk 8 g. butter
Supper	120 g. soup 90 g. meat 120 g. potatoes 90 g. vegetables 90 g. stewed fruit	120 g. soup 90 g. minced meat 90 g. mashed potatoes 90 g. vegetable purée 15 g. butter	120 g. soup 90 g. meat 120 g. potatoes 90 g. milk pudding and stewed fruit
9 p.m.	180 g. milk	180 g. milk 15 g. ovaltine 15 g. sugar	180 g. milk 15 g. sugar

Comparison of Home and Oversea Cases

Of the 61 cases concerned in the experiment, 23 (8 of these were air-crew, 7 of whom were officers) had recently returned from North Africa within the prescribed incubation period of 30 days, and can be said to have contracted the disease away from this country. The remaining 38 (7 were air-crew, of whom 4 were officers—1 officer on ground duties was also included) had not left this country. To ensure that the disease of North Africa was no more severe than that contracted here, a comparative test was made. Table III shows the number of cases placed on each diet from home and overseas service. It is clear that precisely the same proportion of these two groups were on the experimental and the control diets.

TABLE III

	Experimental Diet	Control Diet	Total
Home cases	20 (52.6%)	18 (47.4%)	38
Overseas cases ..	12 (52.2%)	11 (47.8%)	23

This allows a comparison to be made (Table IV) between home and overseas cases without the possible effects of diet interfering. In order that these results should be comparable with those of other observers, the cases have been further subdivided. Those coming under treatment in hospital within one week of the initial symptoms are designated "early" and after this time "late."

TABLE IV.—*Comparison of Home and Overseas Cases. Mean Duration before Return to Normal in Days*

	Late Cases		Early Cases		Total Cases	
	Home	Overseas	Home	Overseas	Home	Overseas
Biliuria	15.0 (9)	12.4 (8)	11.4 (29)	11.8 (15)	12.3 (38)	12.0 (23)
Van den Bergh ..	26.6 (9)	20.4 (8)	24.3 (29)	24.4 (14)	24.8 (38)	22.9 (22)
Hippuric acid ..	16.3 (9)	11.6 (7)	12.8 (28)	12.5 (15)	13.6 (37)	12.2 (22)
Duration of treatment	34.0 (9)	25.8 (8)	32.0 (29)	30.5 (15)	32.5 (38)	28.8 (23)

The number of observations upon which the mean is based appears in brackets.

No significant difference is seen in the duration of any of the standards of fitness from either home or overseas sources. It is therefore considered that the origin of the disease has no bearing on the effects of diets, and, in any case, since those on either diet include equal proportions of home and overseas cases, there can be no error from this source.

The comparative figures for the diet groups are given in Table V.

TABLE V.—*Comparison of Diet Groups. Mean Duration and Standard Deviations in Days*

	Late Cases		Early Cases		All Cases	
	H.P. Diet	Control	H.P. Diet	Control	H.P. Diet	Control
Biliuria:						
Number of cases ..	10	7	22	22	32	29
Mean duration	13.0	14.9	12.5	10.6	12.6	11.7
S.D.	..	..	5.4	4.0	5.2	7.9
Van den Bergh:						
Number of cases ..	10	7	22	21	32	28
Mean duration	24.1	23.0	24.7	23.9	24.5	23.6
S.D.	..	..	9.1	10.2	8.0	12.7
Hippuric acid:						
Number of cases ..	10	6*	22	21	32	27
Mean duration	10.7	20.2	13.8	11.5	12.8	13.4
S.D.	..	..	7.1	9.6	6.8	15.7
Duration of treatment:						
Number of cases ..	10	7	22	22	32	29
Mean duration	28.0	33.1	33.1	29.9	31.5	30.7
S.D.	..	..	12.6	8.4	11.0	12.2

Owing to the small number of cases occurring in the late series the standard deviation has been omitted.

* This figure includes 1 case in which the liver function was subnormal throughout hospitalization.

From Table V it is seen that cases coming under treatment late are small in number and unevenly divided, whereas those coming under treatment early are equally divided. In comparing results there does not appear to be any difference between late and early groups. This is surprising, but may be explained by the fact that only those patients who did not show any immediate response to treatment were transferred from their station sick quarters. These cases tended to be more severe than those in the early series.

Two cases placed on the high-protein diet relapsed. These were both air-crew, and both came under treatment early. The first case—No. 20—relapsed while at the convalescent home. Biliuria was absent and a normal liver function test was obtained before entry to the convalescent home. This patient's second period of biliuria and liver failure has not been included. The second case—No. 8—was discharged from hospital bile-free, the van den Bergh was within normal limits, and the liver function test was normal on discharge. Relapse occurred 11 days later. The second period of hospitalization of this case has not been included, as the object of the experiment is to test the time taken to return to duty.

Case 6, coming late under treatment in the control series, had a prolonged course. Biliuria persisted for 80 days, and the liver function test was still subnormal on discharge.

With so small an experience no significance can be attached to these few individual reactions. In general the evidence given by Table V is that there was no material difference at all between the two diet groups in any of the four characteristics measured.

Discussion

It is possible that the total numbers of cases may be considered to be too small for conclusions to be drawn from these experiments; but it was felt that, since the epidemic period occurs largely during the winter months, care must be taken to include only those from any one winter period, in case of yearly variations in the severity or alterations in the type of the disease.

The importance of even distribution has been recognized in allotting the diet, and statistical analysis has been undertaken to ensure that the use of cases from different areas of infection has not influenced the experiment. It would appear that disease of North Africa in no way differs from that in this country. As Clifford Wilson (1945) has recently stated, the patient's stay in hospital is bound up with many problems

other than their illness; for this reason other criteria have been taken to assess their progress.

The benefit of protein in this disease has largely been based upon the effects of diet in nutritional liver disorders. In the present series it is of interest to note that those on the experimental diet did not show any improvement over those in the control series. This is in striking contrast to the claims made by Beattie (1943-4), who has stated that with hepatitis it was possible to reduce the time spent in hospital by as much as 37% by dietetic measures alone. He further states that, roughly, the average stay in hospital is inversely proportional to the daily intake of protein. It is not clear to which type of hepatitis he refers, nor how much protein is given, but he quotes an average of 150 g. of protein a day in one series—the figure used here.

The active principle in preventing nutritional liver disorders has been traced to sulphur-containing amino-acids, of which methionine appears to be the foremost. It is not possible to determine the methionine content of the diets used in our series, but it is interesting to observe that Wilson *et al.* (1945) and Higgins *et al.* (1945), using oral methionine, were unable to find any statistical difference, using comparable criteria to assess progress.

Macrae *et al.* (1943) have demonstrated that the protein intake of the R.A.F. has exceeded the generally accepted standards of protein requirements. Whether the self-limitation of the disease as shown in Table I is due to the probable protein stores can only be a matter of conjecture. Himsworth and Glynn (1945) have pointed out that the case-mortality rate of the disease of allied pathology—post-inoculation jaundice—was 2.5% in the cases of Fox *et al.* (1942), whereas that in the cases of Findlay *et al.* (1944) it was 1.5%, the difference being considered to be due to the relatively poor nutrition of Fox's cases. This may suggest that the effect of protein is maximal as a protective but not as a restorative measure, and that, as protein deficiency is not found in the R.A.F., this may be the reason for the similarity of the two series. It is clear, however, that no harm arises as the result of the increased protein, and, in the meantime, a further experiment on similar lines is being undertaken with widely divergent protein intakes.

Summary

The progress of 61 cases of infective hepatitis in the R.A.F. is assessed; 32 were treated with high-protein diet with added vitamin B complex and liver extract; 29 were on a control diet. No response to this form of therapy is noted. Two cases relapsed following the high-protein vitamin B diet.

The recovery rate of a series of cases of jaundice due to icterogenic yellow fever vaccine is compared with a series of cases of infective hepatitis.

No difference has been found between the course of cases from North Africa and those from this country.

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CIVILIAN DYSPEPSIA

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Service reports leave no doubt that dyspepsia is an important medical problem of the war, and the purpose of this paper is to show that the same problem exists at home. The present series of cases covers two years—1943 and 1944—at a hospital which serves a large industrial and poor residential district in Greater London. All patients with dyspepsia were referred to the special dietetic out-patient department or to the dietetic wards under our care. Both the surgical and the medical complications of peptic ulcer were admitted to our department, and therefore a satisfactory perspective of the peptic ulcer problem was obtained. A small number of ulcer patients remained in other wards but were fed from the diet kitchen and have been added to our series; probably 98% of dyspepsia cases attending the hospital are included in our figures. The dietetic department has been working eight years, and therefore the figures represent an equilibrium which has been established with the district. A detailed history and examination were recorded in all patients, and are available for further analysis. Barium meal examinations were made in nearly every case, and gastroscopy was freely used in trying to achieve an accurate diagnosis. The clinical material is summarized in Table I. The series does not include about 200 patients referred from other hospitals for gastroscopy.

"X-ray-negative" Dyspepsia

Of all new patients with gastric symptoms 59% have a peptic ulcer. The large group of non-ulcer dyspepsias (41%) will be the subject of a later report, and only a brief account of them will be given. First there was a small group of patients with obvious air-swallowing or nervous vomiting. Secondly, various physical causes may be finally diagnosed—e.g., chronic gastritis, gall-bladder disease, carcinoma ventriculi, early congestive heart failure, pulmonary tuberculosis, diaphragmatic hernia, or habitual purgation. In the majority of cases no definite diagnosis could be given, and they include all degrees of dyspepsia from slight occasional discomfort to regular remittent dyspepsia. At least half this group gave histories suggesting peptic ulcer, and sometimes a subacute gastric ulcer was found gastroscopically. We believe they are indeed peptic ulcer subjects, and correspond with the many patients with proved ulcers (especially duodenal) who give a history of having had a previous negative barium meal examination. Many of these dyspepsia cases seem to arise from the same factors that favour peptic ulcer—the rush and hurry of modern life, with its fatigue, worries, irregular meals, and nervous tension. Modern civilization provides good opportunities for the energetic and conscientious constantly to irritate their stomach. The intensity and duration of the stimuli may determine whether there is only irritability of the stomach or duodenum or a peptic ulcer is in process of formation.

It is worth noting that, although gall-bladder disease was constantly being looked for and many negative cholecystograms were being obtained, in only 23 (5 males and 18 females) out of 1,522 patients was there good evidence of cholecystitis or cholelithiasis; and as a cause of women coming to hospital with dyspepsia, duodenal ulcer (91 cases) was five times as common as gall-bladder diseases. These figures do not include the patients admitted to other wards with biliary colic or jaundice, but, even so, during 1944 the Medical Research Council Classification of Diseases Register (in-patients only) showed only 34, 20, and 4 admissions for the groups 545 (cholecystitis), 546 (cholelithiasis), and 547 (other gall-bladder diseases) respectively.