2. Eine erhöhte Ausscheidung von ^{131}T im Stuhl wurde bei diesen Patienten beobachtet. Insofern hat der Test für diese Gruppe diagnostische Bedeutung.

3. Festal bewirkte einen bemerkenswerten Effekt auf den Absorptions-Test bei dieser Gruppe von Patienten, ebenso bei der Kontrollgruppe von Personen mit ausreichender Verdauung.

4. Symptome, welche zu unzureichender Verdauung führen (insbesondere Meteorismus) konnten durch Festal gebessert werden.

5. Die Stuhlzusammensetzung wurde durch die Anwendung von Festal ebenfalls verbessert.

6. Festal zeigte keine Nebeneffekte.

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Alimentary Production of Gallstones in Hamsters

10. The effect of orally ingested bile acids on development of cholesterol gallstones in hamsters fed a fat-free diet with glucose as carbohydrate component*)

By HENRIK DAM and FREDE CHRISTENSEN

With 3 tables

(Received January 12, 1962)

Formation of cholesterol gallstones in young hamsters takes place with great regularity when the animals are reared on a fat-free diet in which the carbohydrate source is an easily absorbable sugar such as glucose (DAM and CHRISTENSEN, 1961 a, b, and the present communication).

With a basal diet of this composition the efficacy of dietary additions in preventing formation of cholesterol gallstones can be tested, so that only the most active substances will show a marked effect.

In the present study five different bile acids: cholic, deoxycholic, dehydrocholic, lithocholic and hyodeoxycholic acids have been tested in this way at a dietary level of 0.1 per cent.

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Experimental

The animals were golden hamsters from our own stock colony, 31 to 37 days old at the beginning of the experimental feeding period which lasted maximally 55 days.

The composition of the basal diet was as indicated in Table 1.

Table 1. Composition of the basal diet

	g
Glucose	74.3
Vitamin Test Casein*)	20.0
Salt mixture (U. S. P. XIII no. 2)	5.0
Vitamin mixture**)	0.5
Choline chloride	0.2

*) Genatosan Ltd, Loughborough, England.

**) Biotin, 0.050 g; folic acid, 0.050 g; ascorbic acid, 5.000 g; thiamine hydrochloride, 5.000 g; riboflavin, 5.000 g; pyridoxine hydrochloride, 5.000 g; calcium pantothenate, 5.000 g; nicotinic acid, 8.000 g; inositol, 15.000 g; p-aminobenzoic acid, 35.000 g; vitamin K ("Synkavit", Roche), 1.000 g; dl-α-tocopheryl acetate ("Ephynal", Roche), 5.000 g; and sugar up to 500 g.

Vitamins A and D_3 were furnished in the form of an aqueous solution of the following composition: Vitamin A concentrate, 0.62 g (1 g $\sim$ 1.67×10^6 I. U.); vitamin D_3, 0.051 g in vegetable oil (1 g $\sim$ 2×10^6 I. U.); Tween 80, 2.5 g; BHT (antioxidant), 0.03 g; citric acid, 0.1 g; sorbic acid, 0.5 g; distilled water to make 500 ml. 0.1 ml of this suspension was given twice a week, corresponding to 59 I. U. vitamin A and 5.8 I. U. vitamin D_3 per animal per day.

Twenty-nine hamsters (15 males and 14 females) received the basal diet without addition, whereas five groups of 18 to 20 hamsters (7—10 males and 13—8 females in each) received the basal diet with addition of 0.1 per cent of the bile acids to be tested[1]).

Otherwise the details of the experiment were as previously described (1, 2).

Results and Discussion

The results are presented in Tables 2 and 3.

Table 2 contains the recordings for the individual animals.

Table 3 presents a summary of the frequency of cholesterol gallstones in the animals surviving more than 10 days.

Only 2 animals died before the 10th day, but many died or had to be sacrificed before the end of the planned experimental period of 55 days, because they had diarrhea[2]). It is seen from Table 2, however, that with the basal diet used in the present experiment cholesterol gallstones developed so early that shortening of the feeding period was not a matter of great importance. We therefore consider it justifiable to conclude that the addition of 0.1 per cent hyodeoxycholic acid to the basal diet afforded a marked degree of protection against formation of cholesterol gallstones, whereas a similar effect could not be observed for any of the other bile acids tested.

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[1]) The cholic acid used in this experiment was from Eastman Kodak Company, Rochester, N. Y.; deoxycholic, dehydrocholic, lithocholic and hyodeoxycholic acids were obtained from Nutritional Biochemicals Corporation, Cleveland, Ohio.

[2]) As mentioned previously (2), the diarrhea influences the development of gallstones only by shortening the feeding period. (Animals with diarrhea are always sacrificed on the day when the disorder is observed).

Table 2.

Influence of five different bile acids on formation of gallstones when

Basal diet without addition					Basal diet + 0.1% Cholic acid					Basal diet + 0.1% Deoxycholic acid				
Animal number	Days in exper.	Weight gain (g)	Diarrhea	Gallstones	Animal number	Days in exper.	Weight gain (g)	Diarrhea	Gallstones	Animal number	Days in exper.	Weight gain (g)	Diarrhea	Gallstones
Males					Males					Males				
53	16	1*	+	C	111	7	— 3		0	66	31	14*	+	C
50	21	13*	?	C	104	24	— 1	+	0	40	40	— 5	+	C
82	21	13*	+	C	57	25	—11	+	C	95	41	7*	+	C
64	23	10*	0	C	15	28	—12	+	C	3	53	9*	0	C
68	23	10*	+	C	17	29	6	+	C	4	53	8*	0	C
107	23	12*	+	C	33	29	— 3	+	C	75	53	6*	+	C
67	26	10*	+	C	69	29	9	+	C	100	53	18*	0	C
37	28	10*	+	C	21	32	7*	+	C	16	55	15	0	C
65	28	9*		C	83	32	— 7		C	18	55	18	0	C
29	48	14	0	C	101	35	— 5	+	C	35	55	6	0	C
45	48	15	0	C										
47	48	20	0	C										
87	48	17	0	C										
102	48	— 3	0	C										
96	48	— 1		C										
Females					Females					Females				
57	11			CA	32	21	—15	+	0	86	7	—14	+	0
7	48	11	0	C	46	25	9*	+	C	27	12	10*	+	C
19	48	17	0	C	97	28	—18	+	0	36	19	— 1*	+	C
27	48	19	0	C	11	31	9*	+	C	56	27	7*	+	C
97	48	9	0	C	10	33	2*		C	71	34	1*	+	C
40	49	12	0	C	59	35	9*	+	C	82	35	— 2	+	C
4	49	11	0	0	64	40	7	+	0	106	35	— 1	+	C
55	49	18	0	0	89	40	7*	+	0	78	48	13	+	0
61	49	19	0	C	54	44	13*	+	C					
77	49	8	0	C	96	45	9	0	C					
89	49	— 7	0	C										
8	55	— 6	0	C										
81	55	11	0	C										
106	55	18	0	C										

C means that the animal had cholesterol stones only.
CA means that the animal had cholesterol stones and amorphous pigmented stones.

As far as statistical treatment of the results is permissible, a calculation [according to (3)] shows that the probability is well below one per cent for the chance occurrence of the observed difference in frequency of cholesterol stones in the hamsters on the basal diet and in those on the diet with 0.1 per cent hyodeoxycholic acid.

Table 2 (Continuation)

added to the basal "fat-free glucose diet" in the amount of 0.1%

Basal diet + 0.1% Dehydrocholic acid					Basal diet + 0.1% Lithocholic acid					Basal diet + 0.1% Hyodeoxycholic acid				
Animal number	Days in exper.	Weight gain (g)	Diarrhea	Gallstones	Animal number	Days in exper.	Weight gain (g)	Diarrhea	Gallstones	Animal number	Days in exper.	Weight gain (g)	Diarrhea	Gallstones
Males					Males					Males				
80	27	9*	+	C	30	25	— 4	+	C	24	47	16	0	0
38	32	9*	+	C	19	26	9*	?	C	61	47	15	0	0
47	33	12*	0	C	107	28	3*	0	C	84	47	4	0	0
109	40	—10	+	C	23	42	—13	+	C	98	47	10	0	0
1	48	29	0	C	68	48	9	0	C	7	50	15	0	C
6	48	4	0	C	60	55	4*	+	C	31	50	14	0	0
25	48	10*	0	C	65	55	2	?	C	39	50	— 3	0	0
52	48	22	0	C	74	55	4	+	C					
92	48	22*	0	C										
Females					Females					Females				
48	23	6*	+	C	41	21	— 5*	+	C	42	39	— 9	+	0
5	24	— 9*	+	C	44	28	— 4	+	C	45	40	7*	+	0
34	25	5*	+	0	93	29	1	+	C	28	42	—11	+	0
49	27	2*	+	C	79	42	4	+	C	22	45	6*	+	C
51	28	2*	+	C	87	46	5	+	C	14	47	— 2	+	0
67	29	6*	+	0	37	51	6*	?	0	20	47	3	0	0
88	29	1*	+	CA	103	53	14	+	C	50	47	9	0	0
110	33	7*	+	C	2	55	19	?	C	58	47	— 1	0	0
90	34	13*	+	0	53	55	6	0	C	72	47	11	0	0
70	35	— 8	+	0	77	55	17	0	C	73	47	— 5	+	0
105	35	— 3	+	C	108	55	— 7	0	C	85	50	5	0	0
										91	50	0	+	0

The animals were weighed only once a week. An asterisk after the figure indicating the weight gain during the experiment means that the last weighing day was in the week before the day when the animal was sacrificed, otherwise the last weighing took place on the day of sacrifice.

The occurrence of cholesterol gallstones was less frequent among the females than among the males. This difference, however, was of low significance.

It is likely that some of the other bile acids tested would have shown protective effect if they had been given at a higher dietary level, or if the basal

Table 3. Summary of Table 2 with respect to frequency of cholesterol stones in animals surviving more than 10 days

Addition to basal diet	None			0.1% cholic acid			0.1% deoxycholic acid			0.1% dehydrocholic acid			0.1% lithocholic acid			0.1% hyodeoxycholic acid		
	Total no. of animals	Animals with cholesterol stones no.	%	Total no. of animals	Animals with cholesterol stones no.	%	Total no. of animals	Animals with cholesterol stones no.	%	Total no. of animals	Animals with cholesterol stones no.	%	Total no. of animals	Animals with cholesterol stones no.	%	Total no. of animals	Animals with cholesterol stones no.	%
Males	15	15	100	9	8	89	10	10	100	9	9	100	8	8	100	7	1	14
Females	14	12	86	10	6	60	7	6	86	11	7	64	11	10	91	12	1	8.3
Total	29	27	93	19	14	74	17	16	94	20	16	80	19	18	95	19	2	11

diet had been so composed that the tendency to formation of cholesterol gallstones in the control group was less marked. Thus, in two earlier experiments with 10 animals in each group and a basal diet containing 2% lard and having sucrose instead of glucose as carbohydrate component, 0.1% deoxycholic acid protected against cholesterol gallstones, whereas the protective effect of cholic acid was less certain.

Considering the observed high potency of hyodeoxycholic acid in counteracting cholesterol gallstone formation it is of interest to note that Howe, Bosshardt and Huff (4) have found that hyodeoxycholic acid was more effective than lithocholic in neutralizing the hypercholesteremic effect of cholic acid.

The bile acids do not seem to have had any material influence on the growth of the animals which is usually poor on the basal diet, nor do they seem to have altered the tendency to diarrhea which often occurs in hamsters fed a diet with a high sugar content.

Summary

A fat-free diet in which the carbohydrate component consists of glucose is particularly suited for rapid and regular production of cholesterol gallstones in young hamsters.

Testing of the ablity of substances to counteract dietary formation of cholesterol gallstones can be carried out under the strictest possible conditions known when the composition of the basal diet fallows the above principle.

In a test of this type the addition of 0.1 per cent hyodeoxycholic acid to the basal diet afforded a high degree of protection against cholesterol gallstones, whereas a similar protection could not be demonstrated when cholic, deoxycholic, dehydrocholic or lithocholic acids were given at the same dietary level.

In earlier experiments with a basal diet containing sucrose instead of glucose and in addition 2 per cent lard, 0,1 per cent deoxycholic acid protected against cholesterol gallstones, whereas it was less certain that cholic acid at the same level was protective.

Zusammenfassung

Eine fettfreie Nahrung mit Glucose als Kohlenhydratkomponente ist besonders geeignet um Cholesterin-Gallenstein-Bildung in jungen Hamstern regelmäßig und in kurzer Zeit zu entwickeln.

Die Prüfung von Substanzen auf Schutzwirkung gegen alimentäre Cholesterin-Gallenstein-Bildung ist besonders scharf, wenn die Grundnahrung nach dem oben erwähnten Prinzip zusammengesetzt ist.

In einem Versuch von diesem Typ zeigte Hyodesoxycholsäure in einer Menge von 0,1% der Grundnahrung sehr gute Schutzwirkung, während Cholsäure, Desoxycholsäure, Dehydrocholsäure und Lithocholsäure in der Menge von 0,1% der Nahrung keine sichere Schutzwirkung erkennen ließen.

In früheren Versuchen, wo die Grundnahrung 2% Schweineschmalz enthielt, und die Kohlenhydratkomponente aus Saccharose bestand, zeigte Desoxycholsäure in einer Menge von 0,1% der Nahrung gute Schutzwirkung, während die mit 0,1% Cholsäure erreichte Schutzwirkung weniger sicher war.

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Aus dem Physiologischen Institut der Universität Bonn
(Direktor: Prof. K. Wachholder †)

Die Einwirkung einer fettreichen Mahlzeit auf die Gerinnbarkeit des Blutes

I. Bei fettarm und bei fettreich sich ernährenden (fettungewohnten und fettgewohnten) jungen Leuten*)

Von K. Wachholder †, H. Egli, K. Kesseler, H. Buscha und E. Felderhoff

Mit 5 Tabellen

(Eingegangen am 26. Januar 1962)

Einleitung und Fragestellung

Die starke, seit einer Reihe von Jahren anhaltende Zunahme von Herzinfarkten hat zu einer Flut von Veröffentlichungen mit Überlegungen und Untersuchungen über die Gründe dieser auffälligen Erscheinung geführt. In diesen spielt die Arteriosklerose (Atherosklerose, Atheromatose) eine besondere Rolle, für deren Pathogenese Einflüsse seitens eines erhöhten Lipoid- bzw. Cholesteringehaltes des Blutes im Sinne der alten Imbibitionstheorie der

*) Durchgeführt dank einer Unterstützung seitens der Deutschen Forschungsgemeinschaft.