

Material and Methods

61 male and 69 female Eskimos, aged more than 30 years, —hunters and/or fishermen, and their wives— were examined. Blood-specimens were drawn in the morning after at least 10 hours of fasting. Plasma was immediately separated. The following examinations were carried out: plasma-total-lipid was determined gravimetrically after extraction by the method of Folch et al.⁴; cholesterol was determined with a Liebermann Burchard reaction⁵; triglycerides were determined by an enzymatic glycerol estimation.⁶ These analyses were carried out after return to Denmark (2 months later), the plasma-specimens having meanwhile been kept frozen at -20°C .

Quantitative plasma-lipoprotein electrophoresis was carried out on the spot within 12 hours after collection of blood, as the lipoprotein pattern may change with longer delay. The plasma-specimens were kept in ice-water until electrophoresis. The technique, using agarose-gel and quantitative evaluation of the different fractions, were those of Dyerberg and Hjørne.^{7,8}

Results

The concentrations of plasma total-lipids, cholesterol, and triglycerides in the two sexes in different age-groups are given in table I together with the values found in healthy Danish individuals.⁹

Table II shows the results of quantitative lipoprotein electrophoresis with corresponding values from healthy Danes.

It will be seen that there was a very clear difference

in most of the types of lipid between Eskimos and healthy Danes, the concentrations in the Eskimos being clearly and significantly lower than in the Danes. The difference was found to increase with increasing age. The sex difference in some plasma-lipid types (cholesterol, triglycerides, pre- β -lipoproteins) described by several investigators^{9,10} in Western Europe was not found in the Eskimos.

Discussion

The incidence of "atherosclerotic heart disease including coronary arterial disease" (Annual Health Report from Greenland) in the years 1963 to 1967 has been evaluated by the Danish medical officers of the Umanak district. Only 3 cases of these diseases were reported.¹¹ This figure can be regarded as a reliable index. The communication between the medical staff in Umanak and the population in the small remote places is surprisingly good. In each place there is a midwife or nurse who will communicate—mostly by radio—with the hospital in Umanak, and all severe cases of disease will be reported and examined, mostly after admission to the hospital.

Not a single established case of diabetes mellitus is known at present in the population of the Umanak district; this disease is extremely rare in Greenlanders¹² in general.

In the Eskimos the association of low level of most types of lipid (except α -lipoproteins) with very

TABLE I—PLASMA-LIPIDS (g./l. \pm S.D.) IN ESKIMOS COMPARED WITH DANISH CONTROLS

Age (yr.)	Eskimos (n)	Total lipid			Cholesterol			Triglycerides		
		Eskimos	Danes	Sign. of diff. (p)	Eskimos	Danes	Sign. of diff. (p)	Eskimos	Danes	Sign. of diff. (p)
<i>Males:</i>										
31-40	16	6.01 \pm 0.99	6.33 \pm 0.73	n.s.	2.16 \pm 0.29	2.45 \pm 0.37	n.s.	0.58 \pm 0.38	1.01 \pm 0.45	<0.005
41-50	11	6.41 \pm 1.17	7.46 \pm 1.60	<0.05	2.39 \pm 0.41	2.84 \pm 0.59	<0.01	0.55 \pm 0.23	1.53 \pm 0.69	<0.001
51-60	14	6.46 \pm 1.02	7.33 \pm 1.28	<0.02	2.54 \pm 0.41	2.83 \pm 0.48	<0.05	0.54 \pm 0.19	1.27 \pm 0.63	<0.001
\geq 61	20	5.95 \pm 0.56	7.23 \pm 1.17	<0.001	2.29 \pm 0.34	2.75 \pm 0.51	<0.001	0.60 \pm 0.28	1.35 \pm 0.73	<0.001
All	61	6.17 \pm 0.89	7.12 \pm 1.24	<0.001	2.33 \pm 0.35	2.73 \pm 0.49	<0.001	0.57 \pm 0.28	1.29 \pm 0.62	<0.001
<i>Females:</i>										
31-40	19	5.71 \pm 0.93	6.57 \pm 1.24	<0.02	2.03 \pm 0.48	2.48 \pm 0.44	<0.005	0.36 \pm 0.13	1.04 \pm 0.62	<0.001
41-50	16	6.18 \pm 0.91	6.81 \pm 0.97	<0.05	2.30 \pm 0.58	2.73 \pm 0.47	<0.02	0.42 \pm 0.12	0.93 \pm 0.35	<0.001
51-60	15	6.50 \pm 0.89	7.77 \pm 1.27	<0.001	2.25 \pm 0.32	3.06 \pm 0.53	<0.001	0.48 \pm 0.17	1.02 \pm 0.44	<0.001
\geq 61	19	6.21 \pm 0.86	7.94 \pm 1.23	<0.001	2.31 \pm 0.34	3.12 \pm 0.53	<0.001	0.52 \pm 0.13	1.32 \pm 0.62	<0.001
All	69	6.13 \pm 0.88	7.29 \pm 1.16	<0.001	2.22 \pm 0.43	2.86 \pm 0.49	<0.001	0.44 \pm 0.13	1.08 \pm 0.51	<0.001

n = number of persons examined.

n.s. = no significant difference.

TABLE II—PLASMA-LIPOPROTEINS (g./l. \pm S.D.) IN ESKIMOS COMPARED WITH DANISH CONTROLS

Age (yr.)	Eskimos (n)	Chylomicrons $S_f > 400$		Pre- β -lipoproteins $S_f 20-400$			β -lipoproteins $S_f 0-20$			α -lipoproteins H.D.L.		
		Eskimos	Danes	Eskimos	Danes	Sign. of diff. (p)	Eskimos	Danes	Sign. of diff. (p)	Eskimos	Danes	Sign. of diff. (p)
<i>Males:</i>												
31-40	16	0.31	0.17	0.62 \pm 0.36	1.20 \pm 0.62	<0.001	4.32 \pm 0.87	4.61 \pm 0.85	n.s.	3.48 \pm 1.02	2.84 \pm 0.72	<0.05
41-50	11	0.30	0.21	0.45 \pm 0.41	1.90 \pm 0.87	<0.001	4.58 \pm 1.56	5.22 \pm 1.51	n.s.	4.20 \pm 1.54	2.76 \pm 1.02	<0.01
51-60	14	0.31	0.15	0.41 \pm 0.27	1.76 \pm 0.91	<0.001	4.52 \pm 0.70	5.30 \pm 1.14	<0.005	4.40 \pm 1.62	2.78 \pm 0.80	<0.001
\geq 61	20	0.29	0.22	0.30 \pm 0.26	1.67 \pm 1.00	<0.001	4.23 \pm 0.71	5.22 \pm 1.08	<0.001	4.10 \pm 1.50	2.72 \pm 0.73	<0.001
All	61	0.30	0.18	0.48 \pm 0.31	1.70 \pm 0.86	<0.001	4.38 \pm 0.93	5.11 \pm 1.16	<0.001	4.02 \pm 1.39	2.78 \pm 0.82	<0.001
<i>Females:</i>												
31-40	19	0.36	0.15	0.46 \pm 0.30	1.21 \pm 0.66	<0.001	4.03 \pm 1.00	4.46 \pm 1.35	n.s.	3.32 \pm 1.20	3.56 \pm 0.78	n.s.
41-50	16	0.17	0.14	0.43 \pm 0.35	1.11 \pm 0.45	<0.001	4.56 \pm 0.75	4.94 \pm 1.20	n.s.	4.02 \pm 1.50	3.52 \pm 1.03	n.s.
51-60	15	0.23	0.18	0.39 \pm 0.38	0.96 \pm 0.54	<0.001	4.48 \pm 0.81	5.75 \pm 1.45	<0.001	4.74 \pm 1.90	4.34 \pm 1.02	n.s.
\geq 61	19	0.20	0.24	0.42 \pm 0.32	1.52 \pm 0.83	<0.001	4.75 \pm 1.00	6.02 \pm 1.34	<0.001	3.74 \pm 1.20	3.10 \pm 0.94	n.s.
All	69	0.24	0.18	0.43 \pm 0.33	1.20 \pm 0.62	<0.001	4.45 \pm 0.89	5.31 \pm 1.32	<0.001	3.91 \pm 1.41	3.64 \pm 0.94	n.s.

The small and not normally distributed chylomicron values were not treated statistically.

low incidence of ischæmic heart-disease is striking, but not necessarily causal. It fits well with the finding elsewhere—the Far East, some parts of Africa¹³—of low level of plasma-lipids together with low incidence of ischæmic heart-disease. But in these other parts of the world the low plasma-lipid levels may be explained by the predominantly vegetable and low-fat diet.

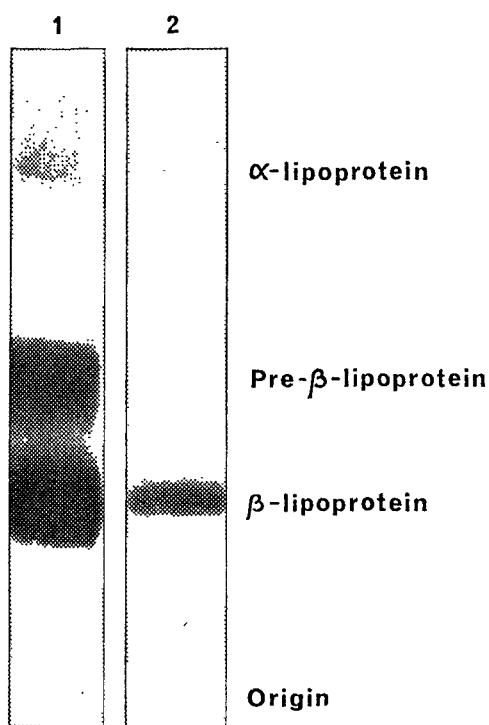
The food of the Eskimos still living as hunters and/or fishermen consists mostly of meat of whales, seals, sea birds, and fish—predominantly Greenland halibut, capelin, and some sort of salmon. This food is extremely rich in protein and fat, and poor in carbohydrates. Potatoes and other vegetables are eaten only in very small amounts. As bread, predominantly some sort of ship biscuit is eaten, and the fluid intake is covered by home-made or Danish beer, and coffee and tea with a good deal of sugar. Dairy products are eaten to a very slight degree.

Krogh, who in 1908 examined the caloric metabolism in Eskimos on the island of Disko close to the Umanak district, stated:

“The normal diet of Eskimos contains an excessive amount of animal protein (280 gr.) and much fat (135 gr.) while the quantity of carbohydrate is extremely small (54 gr. of which more than 1/2 is derived as glycogen from the meat eaten). Their dietary habits are very like those of the carnivorous animals.”³

We believe that the dietary habits of the population in this part of Greenland have not changed much since 1908. (The word “Eskimo” is of Red Indian origin and means “people eating raw meat”.)

The explanation of the rather low level of plasma-cholesterol despite the high intake of animal fat is probably the large amount of polyunsaturated fatty acids in the fat tissue of the animals eaten, which is known to protect against an increasing plasma-cholesterol level.¹³ However, the knowledge of the fatty-acid composition of the animal lipid tissues is limited. The fat meat of salmon is known to contain a large amount of polyunsaturated fatty acids, and it is



Typical lipoprotein electrophoresis strip from a healthy adult Dane (1) and from an Eskimo (2).

TABLE III—PLASMA-LIPIDS (g./l. \pm S.D.) IN GREENLANDIC ESKIMOS COMPARED WITH ESKIMOS LIVING IN DENMARK

Component	Eskimoic women		Statistical comparison (P) (GE/DE)
	Greenland (GE) (n = 35, 31–50 yr. \bar{x} = 40.5 yr.)	Denmark (DE) (n = 25, 27–51 yr. \bar{x} = 38.0 yr.)	
Total lipids ..	5.93 \pm 0.94	7.32 \pm 1.33	< 0.001
Cholesterol ..	2.16 \pm 0.54	2.82 \pm 0.48	< 0.001
Triglycerides ..	0.38 \pm 0.13	0.99 \pm 0.44	< 0.001
Phospholipids ..	2.04 \pm 0.52	2.22 \pm 0.31	n.s.
β -lipoprotein ..	4.27 \pm 0.92	5.00 \pm 1.26	< 0.025
Pre- β -lipoprotein	0.44 \pm 0.32	1.10 \pm 0.67	< 0.001
α -lipoprotein ..	3.64 \pm 1.38	4.24 \pm 1.36	n.s.

yr. = years of age. \bar{x} = mean age.

believed that the composition of animal fatty tissue changes more and more in the polyunsaturated direction as the temperature of the medium in which the animal lives decreases.

Even more striking than the low plasma cholesterol and β -lipoprotein concentration is the low level of triglycerides and consequently of the predominantly triglyceride-carrying pre- β -lipoproteins in the Eskimos compared with the Danes. A most striking and almost monotonous observation was the near-absence of pre- β -lipoproteins on the electrophoretic strips (see accompanying figure). The level of these lipids does not, as in Danish males, increase with increasing age, and the level among the older Eskimos is even lower than that of the younger Danish controls. The metabolism of triglycerides and pre- β -lipoproteins is thought to be closely related to carbohydrate metabolism; and it seems probable that the low level of plasma triglyceride and pre- β -lipoproteins is connected with the extremely low incidence of diabetes mellitus.

The level of α -lipoproteins in Eskimo males was found to be significantly higher than that in Danish males; but there was no such difference between Eskimo and Danish females. The explanation of this discrepancy is obscure.

The cause of the predominantly much lower lipid levels in Eskimos than in Danes could be either genetical or derived from the special Eskimo way of life, including alimentary habits, or both. For some thousand years Eskimos in Greenland have been mixed to a varying and unknown degree, with notably Scandinavians—predominantly Danes, Norwegians, and Icelanders. This fact is illustrated by the blood-groups found in Eskimos.¹⁵ In order to elucidate this problem, the blood-lipid pattern in 25 female Eskimos living in Denmark has been examined (table III). In the levels of most blood-lipids these Eskimos resembled Danes and differed significantly from Eskimos living in Greenland. The levels of serum cholesterol and triglycerides, as well as serum- β -lipoprotein and pre- β -lipoprotein, were substantially higher in the Danish than in the Greenlandic Eskimos. The result of this supplementary investigation points strongly against a genetical and towards an environmental explanation of the very low blood-lipids of the Greenlandic Eskimos.

This work was supported by a grant from Foreningen til Hjertesygdommenes Bekæmpelse and from private sources.

References overleaf

DOUBLE-BLIND TRIAL OF EQUINE ANTITOXIN AND HUMAN IMMUNE GLOBULIN IN TETANUS NEONATORUM

GEORGE H. MCCrackEN, JR.

DUANE L. DOWELL FLORENCE N. MARSHALL

*Department of Pediatrics and Scientific Computer Center,
University of Texas Southwestern Medical School,
Dallas, Texas, U.S.A., and
Hôpital Albert Schweitzer, Deschappelles, Haiti*

Summary 130 infants with tetanus neonatorum were treated on a random basis with either 10,000 units of equine tetanus antitoxin (T.A.T.) or 500 units of human tetanus immune globulin (T.I.G.). 65 infants were in each treatment group. On the basis of mortality, and days in the hospital, days of gavage feeding, and days of sedation for the survivors, there was no significant difference in the treatment groups. The number and severity of complications were comparable for the two groups and no adverse reactions were observed in the 130 infants which could be attributed to either T.A.T. or T.I.G.

Introduction

ALTHOUGH antitoxin has been used in the treatment of tetanus for many years, its efficacy remains in dispute. Many workers have evaluated equine tetanus antitoxin (T.A.T.) in patients of various ages, but few studies have been concerned with the newborn and young infants. The most extensive series of studies was a collaborative project in over 1700 patients receiving either no antitoxin or T.A.T. in dosages from 10,000 to 500,000 units.¹⁻⁵ The first study¹ compared no T.A.T. with 200,000 units; mortality was significantly lower in the treated group. The subsequent trials²⁻⁵ compared dosages up to 500,000 units of T.A.T., and showed that dosages larger than 10,000 units did not achieve mortality-rates significantly lower than that attained with 10,000 units.

Athavale and Pai⁶ administered either no T.A.T. or dosages of 10,000-30,000 units to infants and children with tetanus, and found a significant reduction in the mortality of patients with moderate-to-severe disease receiving antitoxin. There were no differences in fatality-rates among those with mild tetanus or for the three different dosages of T.A.T. used. Similarly, Patel et al.⁷ concluded that antitoxin was of definite value in

the treatment of moderate to severe tetanus, and dosages of 5000-60,000 units did not significantly change the mortality-rate. However, the mortality was significantly increased in patients with severe tetanus receiving no antitoxin or 120,000 units T.A.T.

Although the foregoing studies demonstrated the importance of T.A.T. in certain patients with tetanus, other reports indicate antitoxin has no value. For example, Vaishnava et al.⁸ found no difference in mortality of patients receiving no T.A.T. or dosages of from 10,000 to 60,000 units. The disparity in the results of these studies may in part be due to differences in study design, severity of illness of the patients treated, and the general medical and nursing care provided.

Despite the lack of agreement on the efficacy of antitoxin, it is generally agreed that 10,000 units or more of T.A.T. should be administered to patients with moderate to severe tetanus.⁹ This is especially true in neonatal tetanus, where the severity of illness and mortality is greater than in older infants and children. The only controlled study in which T.A.T. was withheld from patients with neonatal tetanus demonstrated a significantly higher mortality in the untreated group compared with neonates receiving 10,000-30,000 units.⁶ Marshall¹⁰ reported a mortality of 80% in 15 consecutive neonates who did not receive T.A.T., compared with 40% in neonates receiving 80,000 units.

Because antitoxin is administered to almost all patients with tetanus, consideration must be given to the clinical efficacy and safety of the two commercially available preparations: equine tetanus antitoxin (T.A.T.) and human tetanus immune globulin (T.I.G.). No controlled data on T.A.T. and T.I.G. are available to evaluate comparative clinical efficacy. Several groups have reported successful treatment of older tetanus patients with T.I.G.,^{11,12} but there are no studies in the newborn.

It has been estimated that 5-6% of adult patients receiving T.A.T. will have some adverse reaction^{13,14}; 1-4% will develop serum sickness or anaphylaxis.¹⁴ These reactions are rare in the newborn although sensitisation may occur and be manifest on re-exposure later in life. Adverse reactions to T.I.G. are rare in all age-groups.¹³

T.I.G. persists for much longer in serum than does T.A.T.—the half-life of tetanus antibody from T.I.G. in adults is 4-5 weeks, but protective levels (0.01 units per ml.) persist for up to 14 weeks,^{14,15} whereas the half-life for T.A.T. antibody is 1-2 weeks and protective levels are detected for only about 4 weeks.¹⁵ Limited data from newborn infants indicate similar half-life values—about 2 weeks for heterologous antitoxin¹⁶ and 31 days for maternal diphtheria antitoxin¹⁷ and 30-35 days for maternal Rh antibody.¹⁸

Thus, T.I.G. seems to have fewer side reactions and persists in serum for considerably longer than T.A.T., properties which make T.I.G. a potentially more desirable agent in neonatal tetanus. We report here a double-blind controlled trial of 10,000 units of T.A.T. and 500 units of T.I.G. in 130 cases of tetanus neonatorum.

Patients and Methods

The trial was done at the Hôpital Albert Schweitzer in the Artibonite Valley of central Haiti. The hospital serves

DR. BANG AND OTHERS: REFERENCES

1. Sagild, U. Personal communication.
2. Alsbirk, P. H., Schiøler, P. *Ugeskr. Læg.* 1969, **131**, 619.
3. Krogh, A., Krogh, M. *Meddr Grønland*, 1914, **51**, 1.
4. Folch, J., Lees, M., Sloane, S. G. H. *J. biol. Chem.* 1957, **226**, 497.
5. Runde, I. *Scand. J. clin. Lab. Invest.* 1966, **18**, 461.
6. Eggstein, M., Kreutz, F. H. *Klin. Wschr.* 1966, **44**, 262.
7. Dyerberg, J., Hjørne, N. *Clinica chim. Acta*, 1970, **28**, 203.
8. Dyerberg, J., Hjørne, N. *ibid.* 1970, **30**, 407; *ibid.* (in the press).
9. Dyerberg, J., Hjørne, N. Personal communication.
10. Carlsson, L. A., Lindstedt, S. *Acta med. scand.* 1968, suppl. 493.
11. Annual Report from the Chief Medical Officer in Greenland, 1963-67.
12. Sagild, U., Littauer, J., Jespersen, C. S., Andersen, S. *Acta med. scand.* 1966, **179**, 29.
13. Miller, K., Rubenstein, A., Astrand, P. O. *Archs intern. Med.* 1968, **121**, 414.
14. Keys, A., Anderson, J. T., Grande, F. *Am. J. clin. Nutr.* 1959, **7**, 444.
15. Persson, I. *Meddr Grønland*, 1970, **180**, 1.