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TOXIN IN THE FLESH OF THE GREENLAND SHARK

(COMMUNICATION FROM UPERNAVIK AND THE UNIVERSITY ZOOPHYSIOLOGICAL LABORATORY AT COPENHAGEN)

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Of the large numbers of sharks to be found in the waters of the coasts of Greenland, the Greenland Shark (*Somniosus microcephalus*) is the most prevalent. This is a fish with a length of anything from one to four metres. Every year large numbers of this shark are caught with hook and line, with blubber for bait, from boats in the summer months, from the ice in winter. At Angmagssalik there is a special method; the Eskimo makes a hole in the ice and, from a groove at the edge of this hole, allows blood to ooze out into the water; sharks that are lured by the blood are harpooned or simply caught by the eyes and dragged out of the water—a form of sport devoid of all danger, for this shark is incredibly apathetic. I myself have caught a live, unwounded shark from a boat, simply by seizing its tail. Its liver is a valuable commercial commodity, as it contains large quantities of oil; the skin, too, is sold nowadays, one of its uses being for bookbinding. The meat is largely used for dog-feed; the people eat it only when in great need. It is common knowledge that in fresh condition the flesh of this shark is toxic to both dog and man. The symptoms are rather like those of alcoholic intoxication, for which reason the Greenlanders often use the term "shark-sick" of a person who is drunk, and conversely, a poisoned dog they call "drunk", "silaerupok".

I have been unable to observe the symptoms of people poisoned by shark meat, though many Greenlanders told me that this poison does attack man. On the other hand, the symptoms of dogs are described in the literature[1]), i. a. in S. Hjortlund, and I myself have had many opportunities of seeing them.

The syndrome varies very considerably, both as to the violence of the intoxication and as to the symptoms that are most marked. Slightly intoxicated dogs walk about with stiff, slow steps, vomit frequently, and have spurting, watery, fetid diarrhoea, the eyes become red and are turned upwards and laterally. In very slight cases the dog is scarcely ever still, with a wet mouth as a sign of excessive salivation. In most serious cases they are unable to walk, fall over when they

[1]) Det grønlandske Selskabs Aarsskrift 1917, p. 47. — 1918.

attempt to rise, lie with their limbs twitching slightly, and breathe with difficulty, and now and then have brief but violent fits of convulsions; in such cases death often results, apparently from respiratory paralysis. It is my experience that diarrhoea, otherwise such a characteristic symptom of shark-meat intoxication, is nearly always absent in the most serious cases. Finally, I have seen the intoxication manifest its presence by apparently healthy dogs suddenly collapsing and lying with their legs in the air, their bodies convulsed with violent spasms and their backs opisthotonic, while lips and tongue became blue-black. After about thirty seconds the dog dies or it gets up and walks away, apparently only slightly tired.

A number of factors affect the syndrome: the quantity of poisoned meat ingested, and its condition; furthermore, all dogs are not equally susceptible, and gradual habituation sometimes gives a certain degree of immunity from the toxin. Physical work precipitates the appearance of the symptoms; dogs which have eaten shark meat with no ill results become sick when they begin to pull the sledge; after working for a short time they gasp for breath, perspire and salivate, and drop down. After lying quiet a while they may get up and stagger on. Finally, many Greenland dog-drivers believe that the sharks are not equally toxic at all seasons of the year (a matter to which I shall revert), or that the dogs tolerate the toxin better in cold weather.

Shark meat can be detoxicated in various ways. The usual method is to cut it into strips and hang it up in the open air until it is quite dry. The drying process is best and most complete when the meat is hung in winter, so that it freezes stiff; when subsequently it thaws the fluids run from it in large quantities, and in time the action of the sun and the wind dries it right through; presumably the cell walls are destroyed by the frost. If the meat is hung in summer, it forms a crust which prevents the inner parts from becoming quite dry. Badly dried meat of this kind is said to retain the toxin, indeed that it is more poisonous than fresh meat. Some Greenlanders believe that nerve and cartilage tissue is more toxic than the other parts, but I was unable to confirm this. The rough and spiny skin may, if swallowed in large pieces, damage the intestines, but of course this has nothing to do with the toxicity of the meat. When the meat is used for human food it is boiled in three or four waters, which are thrown away; simple boiling is said to be insufficient, which would seem to indicate that the toxin is resistant to boiling, as this form of observation among primitive peoples is usually correct. Some eat the meat in the dried state, or wring the liquid out of it by placing a stick through each end of a strip of meat. The Rev. Peter Rosing of Upernavik, who previously lived many years at Angmagssalik, told me that the people there hung shark

meat in their houses and ate it when some of the fluid had dripped off and it had started to putrefy.

We do not know what toxin it is that Greenland shark meat contains. Rink, whom I quote from Hjortlund's work, was of the opinion that the injurious effect of raw fresh shark meat was a result of its high content of saline liquids, a theory which by the way was expressed to me by a Greenland dog-driver in Upernavik. As I shall show, the entire intoxication syndrome, and the peculiar circumstances under which it is caused, make this theory unlikely. According to Hjortlund, Professor Carl H. Hansen at the Veterinary College performed some experiments with dried Greenland shark meat, which he fed to dogs with completely negative results. Hjortlund had fresh shark meat sent frozen to Copenhagen; the ice was melted before arrival and the meat thawed, and a considerable amount of ammonia had developed. — Hjortlund fed three dogs on this shark meat; they ate large quantities of it with relish, without taking the slightest harm. Thus Hjortlund was unable to demonstrate any toxin either, and he thinks it likely that it is not all Greenland shark meat that is poisonous, or only at certain seasons, or that the toxic substances are so little constant that they had broken down on the way to Denmark.

Though Hjortlund mentions the smell of ammonia, he does not ventilate the possibility that it might be ammonia poisoning. It is well known that even after a short time ammonia forms abundantly in the meat as a consequence of the breaking down of the urea, which is present to an amount of about 2 per cent. (C. Oppenheimer: Handbuch der Biochemie) and which serves to maintain the osmotic pressure.

On account of this smell of ammonia the Greenlanders have credited the shark with a genesis different to that of other fishes; for whereas Hans Egede records that according to the Greenland legend fishes were created from wood shavings, which became fecundated "cum sudore testis", the shark came of a cloth with which a woman dried her hair after washing in urine, and which thereafter was carried by a gust of wind out to sea, where it turned into a shark. That is why, it is added, the shark always smells of urine (i. e. iterok, ammoniacal fermenting urine).

Accordingly, the possibility exists that the high content of urea in shark meat breaks down and forms ammonia in such large quantities as to become toxic. The effects of ammonia poisoning, as described in Heffter's Handbuch der experimentellen Pharmakologie, are not unlike those of shark-meat poisoning. When ammonia as a base or organic salt is injected subcutaneously, or administered by mouth, when absorption is very rapid from the dog's small intestine, the following symptoms appear: Very few minutes after injection the reflex irritability increases,

with advancing motoric debility. Salivation increases, and the dog vomits. At first there are slight clonic twitches in the head and neck musculature. Then suddenly there occurs a violent tetanus of the whole voluntary musculature; the legs extend to the maximum, the back curves opisthotonically. Convulsion of the respiratory muscles stops respiration, which sometimes causes death by suffocation. Or the convulsions relax in time, with jerky clonic spasms and muscle twitches. The reflex irritability, which was quite extinguished during the convulsions, returns and increases beyond the normal, so that sensitive irritants cause fresh and continually weaker fits of tetanic stretching. Very soon there are no more convulsions, and a state of coma sets in, sometimes leading to complete anæsthesia and unconsciousness which may last for hours.

As was shown by GAD ANDRESEN[1]), the urea of fresh muscular tissue breaks down into ammonia; and as a dog at a single meal can consume several kilos of meat, which it swallows in big lumps, there is a possibility that a considerable quantity of ammonia can form in them. Furthermore, as there is much to indicate that the toxin is very volatile and inter alia is removed by open-air drying, it may be that detoxication proceeds through the evaporation of the ammonia. If this theory is correct, it ought to be possible to produce a similar intoxication by giving dogs fresh meat or fish of other non-poisonous animals to which urea has been added. For the purpose of examining this point I made the following experiment:

S., a 4-year old dog, was given 2.6 kg of fresh chopped codfish, the so-called uvak, (gadus ogac Rich.) mixed with 75 gr of urea. It ate the whole greedily. No morbid symptoms.

The same dog, and P, a 5-year old dog, together are given 5.8 kg of fresh chopped uvak mixed with 100 gr urea, and two hours later each received a little uvak. All was eaten with a good appetite, and no morbid symptoms appeared.

T, a four-months' old dog, was given 1.25 kg fresh chopped uvak mixed with 100 gr urea. After eating this it was given the tail of a sea-scorpion, when it vomited about 400 gr of the mince but retained the rest as well as the tail. No morbid symptoms here.

In these experiments no intoxication was produced, which shows either that ammonia intoxication is not the explanation, or that with the method employed the ammonia formed in the animals' stomachs was insufficient. The latter possibility is supported by the fact that chopped uvak + urea in the same concentration as that fed to the dogs had no definite smell of ammonia after standing two days in a jar, whereas some shark meat I had in another jar had a very distinct smell

[1]) Biochemische Zeitschrift 116—266—1921.

of ammonia. Finally, the fact must be remembered that the shark meat is swallowed in large lumps, which may perhaps provide a better opportunity for ammonia to form than that provided by the experiments, in which chopped meat was used; in order to counteract this the dogs in the latter experiments were also given some fish in big lumps but this caused no change in the results.

It was stated above that dogs can obtain a certain degree of immunity by gradual inuration. At places where many sharks are caught the dogs become so accustomed to it that they can eat large quantities of fresh shark meat without coming to the slightest harm. Though it is not poisonous, dried shark meat also seems capable of inuring the dogs, for when after the above experiments with urea and uvak I gave the same three dogs 10 kg of fresh shark meat, which they ate voraciously, they were only slightly affected; their stomachs were much distended, and some hours after the meal they were unusually lively, fought a good deal and got into a state of erotic excitement, but except for this were quite normal. These dogs otherwise were never given fresh shark meat, and lived almost exclusively on dried meat. About two days later the entire team of eight dogs was given 28 kg of fresh shark meat; but beyond marked liveliness they presented no morbid symptoms. In a slightly different experiment, however, I was to see later on that my dogs were not entirely immune from the toxin. Before describing it, however, I must say that other fishes seem to contain a similar toxin, i. e. halibut (Reinhardtius hippoglossides Walb.) and sea scorpion (Cottus scorpius L.); unaccustomed dogs eating quantities of these present the same symptoms as after shark meat. A Greenlander told me that one evening he had fed his dogs on a number of sea scorpions; next morning they were so unwell that they did not move even when kicked, and one of them was dead. My adult dogs have often eaten fresh halibut and sea scorpion without injury, but on the other hand I have been able to produce distinct symptoms of intoxication with sea scorpions. The pup T, 4 months old, was given $^3/_4$ kg of fresh sea scorpion at 6 pm. At 10 pm it was lying listless, but could be made to walk, when it did so naturally; however, its eyes were red and turned upwards and laterally, so that half of the iris was hidden by the superior orbital margin. At 6 am all symptoms had disappeared. Another pup, D., was given half a fresh sea scorpion at 8 pm. At 8 am next day its eyes were turned upwards and laterally, conjunctivae were swollen with purulent secretion and formed a raised border in over cornea. Later in the day the eyes were turned back so far that all one could see was a narrow lower border of sclera covered with swollen conjunctivae. The eyes remained turned up during the following 48 hours, but returned on the third day, and the irritation of conjunctivae disappeared. Except for the eye symptoms

the dog was quite well, a surprising fact, as these eye symptoms usually accompany the most serious cases of intoxication. The sea scorpions used for food contained many pteropods. If this fish is cooked first, even very small pups can eat their fill without incurring any sign of poisoning; the pups referred to above, which were sick after eating fresh sea scorpion, had often been fed on large portions of the same fish boiled; it should be observed that the water in which the fish was boiled was swallowed together with the fish, so that there was no question of any dilution of the toxin, but apparently of its destruction.

According to what the Greenlanders say, people—particularly weak and sick people—may be depressed and lethargic after eating halibut and sea-perch. A Danish official in Greenland told me he always had diarrhoea after boiled halibut. Of a well-known Danish Greenland explorer the manager of the trading post at Tasiussak told me that once while he was visiting him, he turned ill and lay unconscious for several hours after eating fresh raw halibut liver. In this connection it should be mentioned that the liver of the polar bear, the bearded seal and the Greenland dog is poisonous, though I am not in a position to say whether it is the same or a similar poison to that of the shark, the sea scorpion or the halibut. J. LINDHARD[1]) describes an epidemic of poisoning on the Danmark Expedition in March 1907 after eating bear liver. On March 10th they had shot a lean but apparently healthy bear, and next day ate a ragout of its heart, kidneys and liver. They had often eaten bear heart and kidney previously, but not liver, as it was said to be poisonous. The gall-bladder was removed, the liver cut up and washed in several waters, browned in a frying pan and then boiled together with the other ingredients of the meal. The dish was tasty, and they ate a good deal of it. All the nineteen men who partook of it fell ill. The symptoms did not appear directly after the meal, which was taken between five and six o'clock in the afternoon; the first two patients felt ill about nine o'clock that evening, then the majority followed in the course of the evening and night; six of them merely felt there was something wrong next morning when they awoke; one patient, who persistently denied all subjective symptoms, presented objective symptoms on the third day.

The first symptoms included lethargy, tiredness, indisposedness, or an irresistable desire for sleep; this is recorded in seven cases; for most, however, their sleep was restless and broken; one patient had no sleep at all during the first 48 hours. One of the first and most constant symptoms, indicated definitely in 18 of 19 cases, was headache, which almost all described as deep throbbing or piercing pain, and in every

[1]) Hospitalstidende 53—329—1910.

case it was aggravated on moving the head. Most localized the pain to the lower part of the forehead. The pain was persistent, in no case spasmodic, and seemed to culminate after about twelve hours, when it decreased steadily. In one case there was tenderness to pressure on the integuments of the head, in two cases tenderness on the neck muscles. There was also tenderness to pressure on bulbi in four cases, and pain on moving them in six cases. In some there were disturbances of vision; in one case diplopy, in one case flickering which made it impossible to read; and finally, in two cases reddish-yellow or yellowish light before the eyes, one of them very severe and embarrassing; the attacks lasted for some minutes and were associated with pain in bulbi. In three there were tonic and clonic spasms, all in the lower extremities and twice limited to these; in the third case the musculature of the trunk and upper arms was also attacked successively. The attacks lasted from ten minutes to half an hour. The symptoms from the alimentary canal were not very prominent; eleven patients had nausea, only four also with vomiting of mucous, often bile-coloured fluid; in two cases this vomiting was very continuous and distressing during the first 24 hours. There was no diarrhoea. The dogs, which always ate the fresh faeces, during these days evinced a strong dislike for them. The patient most severely attacked showed undoubted signs of cardiac insufficiency. The cardiac dulness was extended laterally, the first heart sound universally of a long blowing character, the second heart sound in the pulmonary area accentuated. The pulse was soft, undulating, very tardy, very irregular in both rhythm and strength. Nothing abnormal in renal function and temperature. During the second 24 hours the skin began to peel round the mouth of several patients; it was like bran, patchy and gradually spread over large areas. On some of the patients this desquamation occurred only on the face, whereas on others it was universal and the patches larger. In all, the skin peeled on ten of the nineteen patients; in one case it seemed to be the only symptom. The two most seriously attacked were well on the 6th day.

The curate Jørgen Brønlund, who was away from home on this occasion, told Lindhard later that Greenlanders never eat the liver of bears, foxes or dogs, whereas they do eat the liver of marine mammals (including walrus and narwhal) with the exception of the bearded seal (*Phoca barbata*), which is considered to be unhealthy; more particularly they avoid the liver of old animals. He said that after eating the liver of this animal the skin begins to peel on the second or third day, commencing in the folds of the skin, i. a. inguina, and then spreading over the whole body. Dogs eat the liver of beasts of prey only when there is nothing else, but nothing is known of their being sick after it. To this I may add that one day I threw a fresh but cold liver of a dog that

had died of shark-meat poisoning to some starving dogs belonging to a Greenlander; they dashed up to it, but left it after sniffing at it, and it lay untouched all the next day, though these were dogs that were thankful to get almost anything. Unfortunately I knew nothing at the time of the theory of the toxicity of dog liver, and omitted to try these dogs with other forms of dog flesh. Brønlund states that one becomes as if "drunk in the head" after eating fresh shark meat, and according to Lindhard this has also been observed by Danes at Ivigtut. Lindhard quotes several earlier authors who have substantiated the toxicity of bear liver (Kane and Peyer, among others), who also mention the skin symptoms. I am unable to say anything as to the cause of the toxicity of bear liver.

It will be seen that as regards some of these arctic animals and fishes, which to some extent live on the same foods, partly direct, partly indirect, there are toxic substances in organs which usually do not contain them (muscles, liver). The question is therefore whether or not it is the same toxin? On the other hand, though the symptoms of shark-meat and bear-liver intoxication are fairly familiar, it is difficult to make comparisons, as shark-meat poisoning has been studied thoroughly on dogs only, and bear-liver poisoning on man; judging from the descriptions available it does not seem to be the same toxin. However, one must be cautious about making comparisons of one animal with another, as their tolerance to the toxin may be different. It may be mentioned as a curiosity that fulmars and ravens sometimes become so "drunk" that they can scarcely fly after eating hanging shark meat; this fact is based on my own observations and the statements of several Greenlanders; I have seen them tumbling and flying very erratically.

One point of great interest to an investigation into the nature of shark-meat toxin is the fact that a substance of similar toxic effect seems to be contained in pteropods (*Limacina helicina*), which occur in large quantities on the coasts of Greenland in August and September. At this period one can often see uvaks lying quite motionless in the water for a long time, without moving for either boat or hook. The stomachs of these uvaks contain large quantities of pteropods. The same is said to be true of sea scorpions, which moreover have the reputation of being especially poisonous in this period. Serious symptoms of poisoning appear in eider ducks which have eaten many pteropods. Andreas Lund Drosvad, leader of the experimental station at Prøven, told me of how one day he was out in a motor-boat to shoot "wingless" eiders swimming on the water. He shot one, which dived; a little later three dead eiders came up, though only one was hit. In order to make sure that it was not the shot that had killed the birds, he sailed into the next flock without shooting; they dived, and shortly afterwards

one came up dead. That this was nothing unusual was confirmed by making enquiries among the hunters at Prøven trading post as to whether they had ever had the same experience. One hunter then told us that in September he had paddled his kayak into a flock of eiders lying on the water close to the shore. They dived, and some time later a number of them reappeared with their legs in the air, some half-dead, others so sluggish that he was able to take them with his hands. He collected as many as the kayak could carry. Their stomachs contained pteropods. Thus these poisoned eider ducks have this similarity with slightly "shark-drunk" dogs, that the symptoms appear only when the animals are exposed to strain: diving and sledge-pulling respectively. Having regard to these observations as to pteropods, along with the statements of the Greenlanders that sea scorpions are especially poisonous to dogs when they are full of pteropods, it is advisable for experiments to be made in feeding pups with pteropods to see if this can produce "shark intoxication". It should also be examined whether it is correct that sharks are more poisonous at certain seasons than at others, and whether there is any connection between this and the periodic occurrence of pteropods in shallow and deep water.

I shall now describe some experiments showing that the detoxication of Greenland shark meat by drying is not due to the removal of the toxin, but merely to its inactivation, and that it is capable of being re-activated, presumably by an enzyme contained in fresh tissue. This means possibly that drying merely destroys this presumed enzyme. For example, if a dog is given dried shark meat, which normally is not injurious, and then a few hours later fresh meat or fish, e. g. seal meat or uvaks, which are not poisonous, the dogs become very sick, often much more so than after eating fresh shark meat alone. There is also the curious fact that these cases of poisoning also occur in dogs that are accustomed to fresh shark meat. I have had the opportunity of closely observing several dogs poisoned in this way, and of making an autopsy of three which died of it. As a more detailed description of the symptoms may be of value to the determination of what the toxin is, I shall record them below.

Two dogs, 9 months old, at noon were given some pieces of shark meat which had been hung up to dry for about two months—of the same kind that they usually received and always had thrived on. At 5 pm each was given a freshly-caught uvak weighing about 1 kg. During the night the dogs howled a good deal, but as they were shut in a secure dog-pen they were not seen to until the following morning. By this time they were both in bad condition, especially one which was tied up and had got the chain twisted tight about its neck. When I saw it at 10 am it lay extended on its side; its legs jerked now and then. During

the night it had vomited some shark meat and a little uvak; thin greyish faeces in the snow may have been evacuated by this or the other dog. The dog slavered continuously. The eyes seemed to be fallen in, and were turned a little upwards and laterally, the pupils were elliptic and reacted sluggishly to light. It was unable to stand on its legs when lifted up. Respiration came at irregular intervals, apparently owing to spasms in the respiratory muscles; the chief difficulty was with expiration. Now and then there were slight convulsive fits, the head being bent back and the legs stretched out together, remaining in that position a moment; otherwise the hind legs were slightly flexed. Heart action natural, auscultation of heart and lungs normal. The dog was only partly conscious, but reacted to loud command. There was distinct spasticity of all extremity muscles, especially the extensors, and all the muscles twitched constantly as if shivering with cold. We raised the dog up by the hind legs and pressed its stomach, whereupon it vomited a few pieces of undigested shark meat and a little grey fetid gastric matter. At 4 pm it lay inert, did not react to the human voice, moved its ears when tickled. Respiration laborious and irregular, almost of Cheyne-Stokes type. The eyes were now turned upwards and laterally so much that the iris had disappeared; conjunctivae red and swollen and covering the lower third of cornea. Twice the dog evacuated some few c.c. of sanguinolent urine, but no faeces that day. Death occurred about 6 pm. The dog had a very emaciated or dried-up appearance. During the whole day it emitted an unpleasant, aromatic, amine-like smell.

The other dog was not nearly so seriously affected. It wanted to lie still, and when it was raised up it stood shakily, shivering, with slightly flexed legs; when pushed it walked with stiff, staggering steps. It is this gait that makes poisoned dogs seem drunk, and it is due to the severe spasticity of all the extremity muscles, especially the extensors; thus it was very difficult to flex its legs. There was also resistance to extension, but not so marked, and tail and neck muscles were rigid. Now and then there was a small series of muscular twitches. Twice during the day it evacuated thin, greyish, fetid faeces. At 6 pm the condition was unchanged. This dog had no eye symptoms. Next day it was quite well.

Autopsy of the dead dog: nutrition good, but not fat. Lungs small, not emphysematous or congested. Liver natural but containing much blood. The stomach contained a piece of undigested shark meat, 10 cm long, and a quantity of thin grey fluid. Mucous membrane slightly cadaverous, otherwise not abnormal. Small intestines natural, not distended. Large intestines: some slimy contents, mucous membrane slightly hemorrhagic, perhaps cadaverous. Kidneys natural. Vesica

contained 15 c.c. red sanguinolent urine, the blood vessels at the base much swollen; no hemorrhage in the brain. Tension of eyes natural.

In this case the shark meat was not definitely dry, as already stated, and therefore I afterwards made similar feeding experiments with very well dried shark meat, which as a further control had been used regularly for feeding the same dogs for nine months, without ever causing the slightest intoxication. At 11 am eight adult dogs were each given three pieces of dried shark meat, and again at 8 pm one piece each as well as half of a newly caught uvak and one sea scorpion. At 2 am the youngest dog M., a well-nourished male, was slightly stiff in the legs and unwell. The others were well and unusually lively. At 6 am M. and the leader-dog K., a powerful four-year old male, were rather sick, with definite symptoms of shark meat intoxication. At 9 am M. lay inert with eyes much drawn in and turned upwards. He slavered a good deal, there was constant twitching and intermittent jerks of the extremities, respiration laboured. Consciousness partly dulled, but the dog could be made to react on being touched and called. Heart action normal. At 11 am it vomited some thin yellow fluid, respiration became irregular, lips and tongue became very cyanotic, and during one or two clonic spasms of the extremities the animal died. The heart continued to beat a few times after respiration had ceased.

At 10 am the other very sick dog K. was walking about with shaky, staggering steps away from the house, apparently trying to find an obscure place to lie down and die. The eyes were much drawn in and turned up and laterally, so much that only the lower edge of the iris could be just seen; on lifting the upper eyelid it was seen that the pupil was elliptic. Conjunctivae badly swollen. The animal lay with continuous twitching of legs and body, but now and then walked about with stiff and staggering steps. The animal was conscious. It slavered so copiously that a large pool formed on the ground under its head. At 2 pm it lay inert on the ground with the inside of the lips touching the ground, still with copious salivation. The eyes were now turned up and outwards to the maximum. It still reacted to calls. Constant twitching of the entire body, interrupted now and then by jerks of the extremities. Respiration laboured all the time, and sometimes there were spasms in the respiratory muscles, with brief cessation of respiration and pronounced cyanosis of lips and tongue. Heart steady, regular and strong. The dog by this time looked very emaciated and dried up. Ear reflex lively. As blubber and fish-oil were said to be a good remedy for shark-meat poisoning, we tried to force some fish-oil into it, but only very little was retained. As the spasms were now very marked and respiration greatly laboured, the dog was given a subcutaneous injection of 1.5 cgr. morphine, which gave a good deal of ease. In addition, it was given

1 litre of 0.9 % saline subcutaneously in the region of the loins in order to counteract the great loss of liquid through the salivation. During the day it was given other three litres of saline, and it was possible to keep it alive till 1 am, that is to say thirteen hours longer than the other dog. During the last seven or eight hours it lay quite inert with the entire musculature twitching, showing great spasticity. It passed neither faeces nor urine during the entire day, whereas it vomited twice, throwing up shark meat and fluid gastric contents. Death occurred with the cessation of respiration; by means of artificial respiration it was possible to keep the heart going for several minutes, and it stopped only after I had ceased the respiration motions.

Of the other dogs two were slightly stiff in the legs, lethargic and slavering; in the evening they had quite recovered. Three had no symptoms at all, and finally, one, the dog P., which had been used experimentally in the urea tests, presented quite a remarkable picture: It was moving about apparently quite well, when it was bitten by one of the others. With a yelp it fell and lay on its back, legs in the air, the legs and body violently convulsed; respiration ceased, and the lips and tongue became bluish-black, cyanotic. The fit lasted about a minute, then it receded suddenly; the dog lay for a moment, then got up and ran off. I ran after it, but was not successful in causing a similar attack, and afterwards the dog presented no morbid sign. This case shows that the poison can bring the nervous system into a state of irritation so that the toxic symptoms are produced by an external trauma—a circumstance that is often observed in winter, for apparently healthy dogs become very "shark-drunk" when they begin to pull the sledge.

Autopsy of the two dogs showed that they were fat, so that their emaciated appearance at the termination was due to loss of water owing to the enormous excretion of saliva. Fat dogs are said by the Greenlanders to be very resistant to shark poison, though I was unable to confirm this. To some extent the statement is correct, however, in so far as thin and starving dogs gorge themselves more on the poisonous shark meat when they get the chance than well nourished dogs. The stomachs of both dogs contained remains of shark meat and uvak bones. The intestines were moderately distended and their contents presented nothing unusual, the mesenterial vessels were very full, intestinal mucous membranes natural. Heart, lungs, kidneys and liver normal. In both dogs the bladder was contracted hard and quite empty, though they passed no water while the affection lasted, and one of them was given four litres of saline subcutaneously, which was rapidly absorbed. Brain and spinal cord natural. The eyes were sunk well into the orbits, the pupils turned upwards and laterally.

Some time later I obtained some shark meat that was badly dried, because it had been cut in strips that were too thick; with this I fed

a three year old dog in order to see if it was poisonous. This dog had not previously been used in these experiments and ate 2.2 kg of the meat, which had a very firm yellow crust, whereas inside it was white and had a strong smell of ammonia. The dog took not the slightest harm from it. In another experiment, in which I combined dried shark meat with 14-days' old seal meat and intestines, nothing happened either. Finally, I fed some dogs several times on fresh shark liver alone; they ate so much that one vomited some of it again, but otherwise they did not become ill, except that they evacuated thin greasy faeces, similar to what is the case when they eat large quantities of seal blubber. Nor did shark liver oil cause any toxic symptoms.

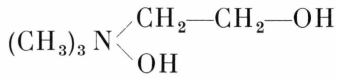
From these experiments it appears that the toxin contained in the meat of the Greenland shark is not destroyed by drying, but only inactivated, and that it is re-activated by the addition of fresh tissue, presumably by an enzyme in the latter. Furthermore, the intoxication produced by dried shark meat together with fresh tissue is if anything more violent than that caused by fresh shark meat alone. The reason of this may be a concentration of the toxin through the drying, or that the dried meat lies much longer in the dogs' stomachs and is difficult to eject by vomiting; as long as thirty hours after a meal I found undigested pieces in the stomach. As I stated above, the slighter cases of intoxication were accompanied by severe diarrhoea, whereas the serious cases were almost constipated, despite loud rumbling and bubbling in the abdomen. The rapid removal of the toxin is undoubtedly of the greatest significance to the prognosis of the case.

The symptoms prove that it must be a nerve toxin with both irritating and paralyzing effects. The psyche is affected; in the initial stages the animals are distinctly excited and lively; in the later stages lethargy sets in, passing into complete unconsciousness. The tonic and clonic spasms, the spasticity and the fibrillary twitchings of the striped muscles show that i. a. the motoric centres in cortex or medulla are brought into a state of increased irritability, a condition which may be latent and require an exterior irritant to make it manifest. Furthermore, a long list of symptoms shows that there is a powerful irritation of the parasympathetic nervous system, viz. the marked enophtalmus and the turning of the eyes upwards and laterally, the enormous salivation, the broncho-constriction, the increased peristaltic and the maximum contraction of the bladder. Death occurs from cessation of respiration; the action of the heart is unaffected till the last, and the heart beats for some time after respiration has ceased.

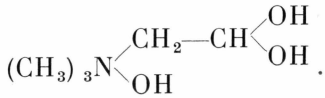
The entire picture of this intoxication is thus very like that produced by muscarine, which occurs i. a. in the fly-mushroom *Amanita muscaria* L. For comparison I shall quote from Heffter's Handbuch der

experimentellen Pharmakologie the description of muscarine poisoning in dogs: First to appear are chewing and licking motions, then profuse salivation, rumbling in the stomach, vomiting, diarrhoea, contraction of pupil. Later they lie on their side, walk only with a stagger. The respiratory frequency increases at first, then decreases; after slight convulsions respiration ceases while the heart is still beating. The bladder may be contracted so hard that it is like a small hard ball. With choline-muscarine there is also marked muscular twitching. To this I may add that among people who eat the fly-mush-room, for example the Samoyedes, who use it as an intoxicant, a state of excitement is brought about, with pugilistic and erotic tendencies—in other words, a mental state similar to that presented by the slightly poisoned dogs.

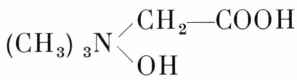
Accordingly, the symptoms indicate that the substance involved in shark-meat intoxication is one closely related to muscarine. One of these is the low-toxic choline,



which occurs in muscle tissue as a component of lecithin, and differs from muscarine only in that it has one oxygen atom more in the molecule:



Betaïne is another oxidation product:



which, together with trimethylamminooxyde $O=N(CH_3)_3$, has been found in shark muscle. Betaïne is also found in fresh squid muscle, in the flesh of the mollusc *Pecten irradians*, the lamprey and the oyster. The slight difference in the molecule of choline and that of choline-muscarine may perhaps explain the curious fact that dried non-poisonous shark meat becomes poisonous when fresh tissue is added, if it is assumed that the latter contains an enzyme which, perhaps through oxidation, transfers the less toxic compound to the toxic. Naturally, the final solution of the problem of the nature of Greenland shark toxin can be arrived at only by means of a chemical analysis of its meat, and it is hoped that this will be made; it would also be interesting to have the pteropods examined. Finally, the question should be taken up of whether atropine, which nullifies the symptoms in muscarine poisoning, has a similar effect on shark-meat poisoning.

Færdig fra Trykkeriet den 11. Juli 1939.