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Nr. 92

THE TOXIC EFFECT OF POLAR BEAR LIVER

BY
KÅRE RODAHL

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A. W. BRØGGERS BOKTRYKKERI A/S

Contents.

Preface.

The present work, which entails a study of the toxic effect of polar bear liver on experimental animals, has been carried out at the Institute of Physiology, Oslo University, during the period October 1947 to December 1948. I am greatly indebted to the head of this institute, Professor dr. med. Einar Langfeldt, for placing the necessary laboratory facilities at my disposal, and for his never failing interest and guidance throughout the entire work, as well as for his valuable criticism and advice during the preparation of this paper.

The material for these investigations was partly collected during the Danish Pearyland Expedition in the summer of 1947, and I wish to express my sincere gratitude to the leaders of that expedition, Count Eigil Knuth and cand. polit. Ebbe Munck, for giving me the opportunity to partake in the expedition. Valuable material was also collected by Captain John Giæver, leader of the Norwegian Summer Expedition to Greenland 1947, to whom I am greatly indebted.

The work has been carried out during a full-time grant from Norsk Polarinstitutt, for which I express my very sincere thanks. My thanks are also due to the head of that institute, Professor dr. phil. H. U. Sverdrup, for his interest and help in the completion of this work. Furthermore my thanks are due to Freiafondet for the grant which they have rendered me.

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Institute of Physiology, Oslo, December 1948.

Kåre Rodahl.

I. Introduction.

1. Information from the Eskimos.

It has been known for centuries among Eskimos and Arctic travellers that the ingestion of polar bear liver by men and dogs causes severe illness.

The belief in the poisonous nature of polar bear liver was probably picked up by early explorers as information from the Eskimos, who never eat it. Stefansson (1921) states that he had been told by many whalers that bear liver was poisonous, but all of them had heard it as hearsay from the Eskimos.

Stefansson gathered from the Eskimos themselves in Northern Canada, that bear liver must not be eaten, and that whoever eats it will become ill. Later on he discovered that what they really meant to say was that bear liver is "taboo" and that some misfortune, perhaps taking the form of illness, would come upon him who eats it as a punishment.

When he asked them as to the nature of the misfortune which might follow the ingestion of the polar bear liver, they said that sometimes the man himself would die and sometimes some of his relatives would die within a year, but that usually the result was whitening of the skin-"leucodermia", a disease said to be common among Eskimos. Stefansson relates that he had once met an old Eskimo whose skin for a larger part had turned completely white, and he was told by several persons that this man had eaten bear liver when he was young.

In accordance with this, Mylius-Erichsen has narrated that the Cape York Eskimos never eat bear liver as a consequence of tradition.

Otherwise Stefansson never met an Eskimo who had ever tried eating bear liver, but he heard from the Eskimos some stories of liver having been given to dogs, who later became sick and eventually suffered from loss of hair.

The belief was that the livers of all kinds of bears were equally dangerous. So strong was the Eskimos' reluctance to eat bear liver that some of them even refused to eat meat which had been cooked in the same vessel where a few slices of liver had previously been fried by Stefansson and his men.

The Eskimos' respect and fear of the bear liver is illustrated by the following stories told by the Norwegian trapper and archeologist Søren Richter (personal communications):

A party of four Eskimos had shot a bear at Flemingfjord in North East Greenland and in order to make sure that their dogs should not get hold of the liver, it was carefully placed on top of the chimney.

On a later occasion, two Eskimos had come to Richter's trapping station at Antarctic Harbour in North East Greenland to fetch a geologist who had spent a few days with him at his hut. At the mouth of the fjord they had shot a bear, and also in this case the Eskimos climbed on to the roof of the hut and hooked the liver on the chimney as high up as possible in order to be quite sure that it was well out of the reach of the dogs.

It is also said that the Eskimos used to throw the livers of polar bears into the sea in order that the dogs should not get hold of them.

On the other hand it is known that dogs are reluctant to eat the liver of polar bear as is generally experienced by the European trappers in North East Greenland with their sledge dogs. Dr. Johannes Troelsen (personal communications) states that once he gave the liver of a polar bear to one of his dogs. As the dog was very hungry he ate a small portion of the liver and subsequently suffered from diarrhea.

He also mentioned that he once observed an Eskimo in Julianehaab who threw the liver from a bear he had shot to three or four of his chicken. The chicken pecked at the liver and subsequently they all died.

In this connection it is interesting to note that ivory gulls and other birds avoid the bear liver (Koettlitz 1898). Even ravens, which are otherwise known for their greediness, hesitate to eat the liver of polar bear, which is evident from the following story told by Captain John Giæver (personal communications): On 1st May 1930, John Giæver met the trapper Thor Halle when he returned to the station "Sverresborg" at Vegasund in North East Greenland. Halle told him that on his last journey, he had found a dead bear on the coast, west of Geographical Society Island.

As he approached the carcase, a raven came out of the abdominal cavity of the bear. He found that the ravens had pecked a hole in the abdominal wall and had eaten all the entrails of the bear. The interesting thing was, however, that the liver was untouched. It was left in its position without a scratch. From the footsteps in the snow around the carcase, it could be concluded that a large number of birds had been there.

The polar bear (Ursus maritimus) is one of the most interesting of all Arctic animals. His proper home is in the pack ice. During the greater part of the year he is constantly on the move, following the edge of the ice where he catches seal in the open water. He stays mainly

in the ice belt along the Arctic coast and congregates where the seals are most plentiful.

His food consists mainly of seal but he can also eat plant material. The polar bear normally eats a certain amount of vegetable food according to Koettlitz (1898) who writes: "They do not eat grass because they are hungry, for I have found seal and grass together in their stomachs and intestines, and observed on one occasion that a bear directly after a meal of seal went three miles for grass, of which it ate a quantity. It appears as though a bear feels a necessity for some vegetable food; possibly health has something to do with it."

The habits of the polar bear are not yet fully known, but it is generally accepted that the female bear hibernates during certain parts of the winter. She digs herself into the snow, making herself a lair where the cubs are born, presumably in the months of January and February. It is said that more often than not she gets twins,and the cubs, when newly born, are not larger than a fully grown rat. Old trappers say that sometimes the male bear, when the weather is particularly bad in the winter, makes himself a lair in the snow for a short period of time. Otherwise he is constantly on the move.

According to Koettlitz (1898) the polar bear was often found to suffer from various complaints. Wounds and scars were frequently seen in the bear, and the wounds were always septic. He also found that fractures of bones were not uncommon. On one occasion he found four fractures in one bear, as well as partially united ribs with a large amout of callus. In several cases he found fractured penis bone with reunion at an angle. Caries, periostitis and swelling of the jaws were seen, and bone deformities and abnormalities such as exostosis, arthritis deformans and osteo-arthritis were not infrequent. In one case he found the bones of all four feet to be considerably enlarged, especially in the neighbourhood of the joints.

2. Experiments by Arctic Travellers, and the Symptoms of Polar Bear Liver Poisoning.

In the Arctic literature there are many communications showing that early Arctic travellers knew about the poisonous nature of polar bear liver.

Richardson (1861) recounts that when members of an expedition led by Barents to Novaya Zemlya in 1596 ate bear liver, they all became ill. In three cases the illness was severe with peeling of the skin from head to foot.

Another early account of this phenomenon was given by Kane (1856) who experimented with bear liver on several occasions, in spite

of the generally accepted view that it was poisonous. In some cases no ill effects were observed, but in other cases sudden poisoning appeared, and the symptoms were described as "vertigo, diarrhea and their concomitants". Kane's first case of poisoning occurred in the month of October. It is known that the dogs on Kane's expedition ate the bear liver without ill effect.

Another example is given by Hall (1876) who wrote with regard to a bear they had shot: "Every part except the liver was good." Moreover, Payer (1877) said about the bear liver: "This liver was thrown into the water."

Later on Payer reports that both Davis and Barents had experienced the poisonous nature of the polar bear liver and he added that the experiment of eating it was repeated on his own expedition with the same unfortunate results.

According to Koettlitz (1898), several members of an English expedition to Franz Josef Land 1894—97 ate polar bear livers on a few occasions and all suffered in consequence.

Four or five hours after the meal a frontal headache occurred which gradually increased, and which did not respond to any treatment. Lying down made it worse instead of better, and sleep was impossible. The headache steadily increased for about six to eight hours, after which the symptoms gradually decreased in severity and at the end of twenty-four to thirty-six hours they were all recovered. Nausea and vomiting ocurred in the cases where much bear liver had been eaten.

Koettlitz adds that eating of bear kidneys in some cases seemed to cause the same symptoms, but in a much lesser degree.

Otto Sverdrup (1903) had repeatedly noticed that the dogs refused to eat bear liver unless they were very hungry. He adds that he had often eaten it himself without becoming sick and he does not believe, therefore, that it is so very poisonous.

J. Lindhard (1913), physician of the Denmark Expedition, gives a detailed and interesting account of poisoning by polar bear liver:

On the 10th March 1907, a bear was shot near the ship in the forenoon. Lindhard states that it was lean but apparently healthy, being more than usually lively and aggressive. On the following day they prepared "ragout" for dinner from the bear's heart, liver and kidneys. Although they had often previously eaten the heart and the kidneys of polar bears, they had never tried the liver before, as they were aware of the opinion that it was poisonous.

After the gall bladder had been carefully removed, the liver was cut into squares and browned in a pan after the pieces had been washed in several lots of water. It was afterwards boiled for a long time with the other ingredients of the dish. The result was quite a well tasting dish and most of the members of the expedition ate a considerable quantity.

The nineteen men who partook in the meal were all sick, including the physician. The symptoms occurred in the first two victims about three to four hours after the meal, which was taken between five and six in the afternoon. The majority of the cases followed in the course of the evening and night.

The first symptoms that appeared were drowsiness, sluggishness, indisposition and an irresistable desire to sleep. This was noticed in seven cases. One of the patients had absolutely no sleep for the first two nights and in most of the cases the sleep was uneasy and broken during the first night.

One of the first and most constant symptoms was headache which occurred in eighteen out of the nineteen cases. The headache was described by most of the patients as deep seated hammering and boring pains, but by a few as tension or pressure. It grew worse by turning the head, by coughing and sneezing, and the pain then spread sometimes to other regions. The headache was found to be persistent and in all cases it seemed to culminate after about twelve hours. After the third day only a few were still feeling pains with sudden movement of the head.

In one case, there was a very great sensitiveness to pressure on the insigment of the head, and in two cases sensitiveness on the muscles of the neck. There was likewise sensitiveness to pressure on the eye balls in four cases and pains when moving the eyes in six cases.

In some of the patients disturbances of the senses occurred. Thus in one case there was double sight, and in one case flickering which made reading impossible. In another case, some extraordinary disturbances of the vision occurred, and finally in two cases reddish-yellowish or yellowish flame sensation occurred, one of which was very strong and troublesome, the effect lasting some minutes and being accompanied by some pain in the eye balls.

Tonic and clonic attacks of cramp occurred in three of the nineteen patients. In all three cases the muscles of the lower extremities were affected and in one of the cases other muscles of the body and the upper arms were also affected in addition to the lower extremities. The cramps were reported to occur intermittently especially in the night, lasting from ten to thirty minutes and the patient was afterwards very tired.

There was little evidence of symptoms of disturbance in the digestive organs. In half of the cases the appetite was reported to be decreased, one had an increased appetite. Most of the patients complained of an indescribable bad taste in the mouth and in two cases the tongue had a light greyish coating. Eleven out of the nineteen patients showed a greater or lesser extent of sickness but only four suffered from vomiting, although these vomitings were very persistent and troublesome during the first twenty-four hours. Diarrhea did not occur but there was constipation in some cases.

Six out of the nineteen men only stated that there was something wrong with them when they woke up in the morning. In one patient, objective signs of sickness were observed on the third day, although he obstinately denied all subjective symptoms.

It may be worth mentioning that the dogs, which otherwise were always very eager to eat the men's feces, showed a distinct dislike to it during this period.

Lindhard reports that the patient who suffered most had eaten an unreasonable amount of the dangerous dish and showed evident signs of heart weakness. He does not state, however, whether the patient previously suffered from any heart weakness. He reports that the dullness over the heart was extended over a larger area than normal. The pulse was found to be weak, undulating, intermittent, very irregular both in rhythm as well as in strength. He reports that in several other cases the pulse was weak but regular. The frequency was in some cases increased, up to 90 per minute, but in one case, reduced to forty-nine instead of the usual sixty to sixty-five.

Lindhard also reports that in two of the most severe cases the micturition was seldom and small in quantity, in other cases it was remarkably frequent with much urine.

He reports that several patients complained of feverish attacks, one of shivering, but in the cases where it was read, the temperature proved to be rather subnormal.

Peeling of the skin around the mouth occurred in the second twenty-four hours in several of the patients. The peeling was described to be scale-like, beginning in spots and gradually spreading over larger areas. In some cases, the peeling was confined to the face, but in several it was universal and thus more serious. In one case, large flakes of skin were still peeling off the hands and feet on the ninth of April, approximately one month after the liver had been eaten. Altogether the peeling occurred in ten out of nineteen patients, in one case it seemed to be the only symptom.

One patient complained of heat sensations and of prickling of the skin. On the first afternoon he was somewhat red and puffy in the face and peeling occurred a good deal later.

The two most serious cases were only completely recovered after the sixth day.

Lindhard considers it certain that this illness was due to the incidence of poisoning due to the afore mentioned dish, in other words, caused by eating the polar bear liver. He states further that there can hardly be any talk of the organs mentioned being putrified at a time of year when the thermometer at night stood about — 40° C.

Stefansson (1921) describes in detail an experiment with bear liver in the spring of 1915 near the North West corner of Banks Island, where

he and three of his men were encamped and where they had killed a polar bear which had been crawling around for a day or two eating the entrails of killed bears and other scraps he found lying about.

The liver was fried in mouldy caribou fat and they found that it tasted even better than seal liver, although the latter is considered by white men to be as good as calf's liver.

Some six or eight hours after the meal, one member of the party awoke with a violent headache in his forehead and eyes and soon he suffered nausea, the vomiting continuing with about half hourly intervals for several hours. A second member of the party was not as ill as the first member described. They both suffered from poor appetites and they described the headache as the worst either of them had ever suffered. Stefansson and the fourth member of the party remained unaffected.

Simultaneously, but unknown to them, two other members of the expedition had carried out an experiment on bear liver. After a supper of fried liver they both awoke some hours before their ordinary breakfast time with the most violent headache either of them had ever had. Vomiting continued all day and they were so sick that even the next day they felt weak and were only able to travel with difficulty, and they said that there was nothing except the bear liver that could be considered as a possible cause of the illness.

With these results in view, another experiment was made on another bear liver from a bear killed at Cape Ross. Previously they had noticed that it was those who preferred the liver underdone who became ill, but this they thought might have been a coincidence.

They had a meal about 10 p. m. and soon after that they went to sleep. Stefansson relates that at about four in the morning one of the party was seized with nausea which continued at half hourly intervals until noon and he had a violent headache. A second member of the party had a slight headache but said that he had a similar headache for two or three days, and believed it to be connected with a slight attack of snow blindness. A third member of the party had a slight frontal headache explained to be seated at the back of the eyes. A fourth member of the party had also a slight headache which became rapidly worse during the forenoon and at noon he became nauseated. The worst period of his illness came about five o'clock. Th following morning some of the party still had a poor appetite while one of them was fully recovered.

Stefansson concludes that fully three quarters of the livers ever eaten by him or others in his presence have had no bad effect. He concludes that certain bear livers are slightly poisonous, while others are not, and he claims that it is possible that thoroughness of cooking has a protective effect.

Fridtjof Nansen (1924) mentions that on two occasions he ate small amounts of bear liver without ill effect. It seems probable therefore, that the poisonous effect only occurs when large quantities are consumed.

A further example of the toxic effect of bear liver when eaten by man is given by L. Breitfuss (1925) in his book: "Irrfahrten im Lande des Weissen Todes" where the diary of Albanow is published. During the Brussilow Expedition 1912—1914 Albanow and his men once ate raw bear liver with salt, and Albanow relates that this dish, which they found to be delicious, had an immediate stimulating effect on the crew. They appeared to be completely changed after the meal, being in good form and spirit. The following day, however, they all (including Albanow) suffered from severe headache and dizziness which to Albanow resembeled the effect of carbon monoxide poisoning.

This was the first time they had eaten bear liver. They were aware of the belief that it was supposed to be poisonous, but did not pay much attention to this. They never ate bear liver again however.

A Norwegian whaler Andreas Ingebrigtsen (personal communications) relates that during whaling off Spitsbergen in 1933, the crew of one of the whaling boats became ill after eating the liver of a polar bear. They had shot a large bear, and as the men were hungry they consumed the whole of the fried liver in a single meal. Shortly after the meal all of them became ill, and it was found that those who had eaten most were more ill than the others. The symptoms described were severe headaches, sickness and vomiting. The illness lasted for forty-eight hours, after which time they had all recovered without any treatment. Later on they were perfectly healthy and partook in the whale catching as usual.,

Arne Høygaard (1937) gives a description of his experiment with eating bear liver during his expedition to South East Greenland in 1936—37. He did not believe that the bear liver was poisonous, as he had heard from several explorers that they had eaten bear liver without ill effect.

He got hold of a liver of a polar bear, and although he was warned not to eat it by the local clergyman, who assured him that the Eskimos knew well what food was inedible, he decided to proceed with the experiment.

The liver was fried by his maid, the Eskimo girl Ipa, who on her voyages to Umivik had learned that the liver of polar bear was poisonous. Later on she told Høygaard that she had seen dogs die after eating bear liver.

At midday, Høygaard had a meal of the fried bear liver, and he says that he ate a great deal. At 5 p.m. he felt no ill effect and went to the hospital to attend to some patients as usual. In the night,

however, he became severely ill. He relates that he had never been so ill before in his life, the symptoms being: dizziness, violent headache, vomiting and diarrhea. This persisted throughout the next day when he still felt very ill. On the third day, there was some improvement and after four days he believed himself to be completely recovered. About a week later, however, peeling of the skin occurred like that which follows scarlet fever, and he also lost some hair. The skin particularly peeled off the face, the feet and hands, and also all over the body.

In the same connection Høygaard relates that an old Eskimo by the name of Knut had confessed to him that once when he was near starvation, he had eaten bear liver and had become severely ill.

The most recent case of poisoning by bear liver has been described by Doutt (1940). Two polar bears were shot near Walter Island by his party on the evening of September 8th. On the following evening the cook prepared fried bear liver and onions. Doutt describes that the first taste of the dish was soapy, but after that it seemed delicious and they all ate a considerable quantity. Doutt himself consumed two slices of the liver, each about 3 by 5 by ½ inches, which may be calculated to weigh approximately 300 grams. About one o'clock the following morning Doutt wakened with a dull headache and sickness. Later on in the day the whole party was sick, those who had eaten most of the dish being the most affected. The symptoms were headaches, nausea, and a sensation of dizziness and torpor. Those who used laxatives seemed to improve more rapidly than those who did not. They were all recovered, however, in the course of two to three days, and none of them experienced peeling of the skin.

3. Livers of Other Arctic Mammals.

a) Poisonous Livers.

Apart from the liver of polar bear, the livers of certain other Arctic mammals are also known to be poisonous, although opinion on this point is less unanimous.

Thus Dr. Troelsen, who had lived several years among the Eskimos at Thule, North West Greenland, relates (personal communications) that the liver of Greenland huskie (Canis groenlandicus), fox (Canis lagopus), wolves (canis lupus) and bearded seal (Erignathus barbatus) are known by the Eskimos there to be poisonous and are never eaten by them. This is said to be a very old tradition. The liver of halibut is also believed to be poisonous.

In accordance with Troelsens report, Dr. A. Bertelsen (1940) states that it is well known to the Eskimos in Greenland that the liver of Eskimo huskie, fox, polar bear (Ursus maritimus), and bearded seal

are poisonous and inedible, as well as meat from Arctic shark (Somniosus microcephalus).

Bertelsen reports that in the year 1891, some Eskimos in the Umanak district had eaten dog liver with ill effect. He describes that during the winter 1890—1891 the seal catch had completely failed at the small Eskimo colony Augpilagtoq, consisting of two houses some distance north of Ikerasak. Bad weather hindered any communication with the outside world and soon the inhabitants were on the border of starvation. They were forced to eat anything edible, even dried seal skins. They were compelled to kill their dogs for food, and finally they were forced to eat the livers of the dogs, in spite of the fact that they knew them to be poisonous. After this they all became seriously ill. When the ice was formed on the fjord, two of the men from the colony finally succeeded in reaching Ikerasak for help. Bertelsen was told by people who took part in the rescue that they could never forget the sight of these people, who were in an appalling condition, and as the Eskimos said: "by the poisoning they had quite lost their hair".

In the same connection, Bertelsen explains how he noticed during a journey in 1908, when repeated mishaps forced them to kill half of their dogs for food, partly for themselves and also for the other dogs, that the very hungry dogs never ate the liver of the other dogs.

With regard to the liver of bearded seal, Lindhard (1913) also states that it is considered dangerous by the Eskimos, and that livers of the older animals are especially avoided. When the liver of this seal is eaten, peeling of the skin takes place in two to three days, beginning in the folds of the skin, in the inguinal region for example, and then spreading over the whole body.

Livers of bearded seals are frequently eaten by Norwegian trappers in North East Greenland, and in some of the cases no ill effects have been observed, although considerable quantities of liver have been eaten.

John Giæver relates (personal communication) that during his stay in North East Greenland in the years 1929 to 1931 and 1932 to 1934, he and his companions ingested considerable quantities of livers of bearded seal several times without any ill effects whatever. This information refers to the time between May and September and the animals eaten have been of various ages from very young to fully grown animals.

The liver of bearded seal is considered by the Norwegian trappers in Greenland to be very tasty. Some of the trappers claim that the liver is the first they eat after the animal is killed.

The seal liver is usually prepared by the trappers in the following manner: During the skinning of the animal, the gall bladder is removed. The liver is cut in thin slices and is fried in margarine in the frying pan. In some cases the slices are left in vinegar for about twenty-four hours

before they are fried. Some of the trappers eat the liver prepared as "beef". In that case it is fried in a frying pan and is afterwards boiled for about half an hour in the sauce. Other trappers prepare the liver as a "steak", boiled in brown sauce in a pan up to three hours.

It is difficult to estimate the amount of liver ingested in one single meal, but Giæver states that it is not unlikely that he has consumed up to half a kilo of liver in one single meal.

Søren Richter and his men (personal communications) once ate a small meal of fried liver of bearded seal without ill effect, but as they did not find it very tasty, they did not eat much — perhaps less than a hundred grams.

Liver of ringed seal (Phoca hispida) is very often eaten by the trappers and is considered by them to be a delicacy, and is eaten without any ill effects.

Richter relates, however, (personal communications) that the Danish wireless operator de Lemos and his party at Ella Island, on two or three occasions had eaten livers of particularly large ringed seals with ill effect. When they became ill the first time, after eating the liver of a particularly large ringed seal, they thought it was only a coincidence and they repeated the experiment, but again they became severely ill with nausea and vomiting and severe headache.

According to Dr. Troelsen (personal communications) the Eskimos in Thule, North West Greenland, also say that the liver of Artic shark is poisonous. Furthermore, the Eskimo clergyman Jørgen Brønlund (Lindhard 1913) also states that sickness follows from eating fresh shark meat, which is also observed by the Danes at Ivigtut. The result is expressed as "giddiness" in the head. On the other hand, Søren Richter reports (personal communications) that members of a Norwegian expedition to Spitsbergen, led by Adolf Hoel, had eaten large quantities of fresh shark meat without any ill effects whatever.

Dogs also suffer from eating shark meat, which is well known among the European trappers in North East Greenland. The symptoms in dogs are sickness, diarrhea, — they cannot walk straight and act as if they are drunk. It is known that the shark meat can be used for human food, however, if it is boiled for three to four hours in water, which must be discarded. The Eskimos eat it when frozen in the snow.

According to Brønlund (Lindhard 1913) the Eskimos also advise against eating deep water fish, such as halibut, by people who are sick or weak or, for instance, pregnant women. The eating of this fish is said to give rise to heaviness and drowsiness and to aggravate already existing complaints. The Eskimos are also acquainted with mussel poisoning.

b) Non-Poisonous Livers.

Livers of all the sea mammals are eaten by the Eskimos, even the livers of walrus (Odobaenus rosmarus) and nar-whale (Monodon monoceros), with the exception of the liver of bearded seal. Troelsen says he has eaten large quantities of walrus liver, altogether approximately 20 kilos, raw as well as boiled, fried and frozen, both from old and young animals without ill effect, and he says it tastes excellent. The Eskimos also eat this liver but they prefer the seal liver. Klutschak (1881), however, states that ill effect may follow ingestion of livers from particularly large male walrus.

Liver from nar-whale is not eaten in large quantities by the Eskimos, but they say it is not poisonous. It is soft and spongy. The skin and the meat as well as the blubber and the intestines from the nar-whales are eaten in large quantities.

II. Own Investigations.

1. Preliminary Investigations.

From the available information it appears that livers of polar bear, bearded seal, and Arctic huskies are toxic to men and dogs. Of the livers mentioned, that of polar bear seems to give most constant rise to toxicity, although it appears from the available information that the polar bear liver does not always prove to be poisonous to human beings. There appears to be no doubt, however, that the bear liver is frequently poisonous, without it being possible to decide from the available information whether or not this is due to any toxic substance normally present in the bear liver. So far there has been little evidence which could elucidate the cause of the toxic effect. It seems evident that no toxic effect occurs when only very small amounts of bear liver are consumed. Furthermore, there is certain evidence of the fact that the toxic effect may be less pronounced when the liver is well fried or cooked (Stefansson). From the available literature, the age and condition of the bear seems to be as irrevelant in this connection as the time of year.

In the case of bearded seal, it is known among the Eskimos that it is the older animals, in particular, which are poisonous. Illness is also reported as the result of eating particularly old and large ringed seal.

It seems evident that the poisonous effect of shark meat is of a different nature to that of bear and seal liver, and the symptoms described are entirely different in the two cases.

The question therefore remains: What is the cause of the ill effect which follows the eating of these Arctic mammalian livers, — and how can it be explained that some of the livers prove to be poisonous when others are not? This was one of the problems that confronted me when, in 1939, I set out on the scientific wintering expedition to North East

Greenland, the chief purpose of which was to undertake some biological investigations at a laboratory established at the trappers station Revet, latitude 74° 30′ N.

With regard to the first question, it is known that the bearded seal constitutes an important part of the food of the polar bear and the liver is one of the first parts of the seal that the polar bear eats. It seems, therefore, likely that if the seal liver contained any toxic substance, it might also accumulate in the bear's liver, — but if so, why is the seal liver not toxic to the polar bear in the same way as it is toxic to human beings?

It will be observed that the symptoms described in the literature as a result of eating large quantities of these livers, are the same whether it is polar bear liver or liver of bearded seal. Of the symptoms described by Lindhard, peeling of the skin is also mentioned by Barents and Høygaard. The same symptoms are also given by Brønlund as characteristic of the illness as a result of eating the liver of bearded seal. It is interesting to note that Lindhard (1913) reports that five of the members of the Danish expedition suffered from severe headaches in the following winter through eating seal liver. In several respects the pains resembled those resulting from poisoning by the bear liver.

Apart from the headache, which seems to be the most prominent symptom in all cases, the peeling of the skin seems to be a frequent symptom, and one of great interest, as it is an objective one.

In none of the cases described, the exact amount of liver ingested in a single meal is reported. In some cases, it has been stated that a large quantity was eaten, and in other cases only small amounts of the liver were consumed. Large quantities of liver may, to some people, mean one hundred grams, and to others, it may mean five hundred grams or more.

In the case described by Lindhard, nineteen men partook in a meal prepared from one bear liver. If the liver weighed five thousand grams and all of it was consumed, it would mean that each man, on an average, consumed approximately two hundred and fifty grams. In the case described by Ingebrigtsen, ten men consumed the whole liver of one bear — which would mean that each man consumed an average of five hundred grams, if the liver weighed approximately the same. The amount of bear liver eaten by Doutt in a single meal has been estimated to be approximately 300 grams.

It may therefore be said that in some cases ingestion of amounts between 250 to 500 grams of bear liver has proved to be poisonous to man.

Apart from the mentioned experiments by Arctic travellers few attempts have been made to investigate the cause of the toxic effect of bear liver.

According to Jackson (1899), V. Harley of University College, London, examined bear liver in order to find the reason for its toxicity. Intraperitaneal and subcutaneous injections of alcoholic, ethereal and aqueous extracts had no toxic action on dogs and guinea pigs, and a dog given an aqueous extract by mouth was also unaffected.

Two mice died three days after subcutaneous injection with an ethereal extract, but it was believed that the result was possibly accidental. Mice were unaffected by injection of alcoholic and aqueous extracts. Thus the experiment offered no solution and the toxicity of bear liver remained an unsolved problem.

Since it was reported that large doses of vitamin A in the form of fish liver oils had a harmful effect on experimental animals, causing the condition of hypervitaminosis A, it seemed possible that the reason for the toxicity of the polar bear liver might be due to a particularly large content of vitamin A which might give rise to hypervitaminosis A when eaten in large amounts. Furthermore, some of the symptoms described by people who had ingested large quantities of polar bear liver resembled to some extent some of the symptoms, such as the skin lesions, produced in experimental rats when given excess of vitamin A. This possibility was raised during a discussion with Professor Einar Langfeldt, head of the Institute of Physiology, University of Oslo, prior to my departure from Norway for the expedition to Greenland in 1939.

The condition of hypervitaminosis A in experimental animals was first described by the Japanese Takahashi, Nakamiya, Kawakimi & Kitasato (1925) and has since been investigated by many workers.

Although it was not considered quite certain that vitamin A itself was poisonous, the toxicity was considered at least closely associated with the vitamin in its concentrates.

The lesions produced in rats have varied remarkably according to the size of the rat, and the magnitude and duration of the overdosage of vitamin A. Skin lesions, ranging from a slight roughening of the hair to seborrhoea and alopecia, are common at all ages. When the vitamin is given in the form of drops of concentrate into the mouth, peeling of the skin at the corners is frequently observed. There may be enteritis, emaciation and pneumonia. More specific lesions, however, are fracturing of the bones, — seen most frequently in growing rats, and profuse and sudden internal hemorrhage, often seen in adult animals.

During my expedition to Greenland 1939—40, specimens of polar bear liver were collected with a view of identifying the toxic substance. It was originally planned that this material should be brought back to Norway for further investigation, but after the invasion of Norway in the spring of 1940, this became impossible and all the material collected during the expedition was brought to England in the autumn of 1940. There I was given the necessary facilities to continue the research at

Dunn Nutritional Laboratories, Cambridge, in collaboration with Dr. T. Moore.

By chemical and biological examination, these specimens were found to be very rich in vitamin A as also was a specimen of liver from bearded seal (Rodahl & Moore 1943). It thus seemed probably that the very high concentration of vitamin A found in the polar bear liver, might be the cause of the toxicity, and that ingestion of large amounts of the liver might lead to hypervitaminosis A.

In order to verify this, various extracts of the liver were given to experimental animals.

The specimens were brought from Greenland preserved in brine. Small portions were digested with alkali and vitamin A was extracted according to the technique described by Davies (1933). Vitamin A was then estimated by the $SbCl_3$ method, using a factor of 0.6 for the conversion of blue units into international units (I. U.) (Moore 1937).

The first bear liver to be examined by Rodahl and Moore was taken from a two year old female and contained 18,000 I. U. of vitamin A per gram of wet material. A second specimen was taken from a four year old male and contained 18,000 I. U. of vitamin A per gram liver. From a third specimen collected by Captain Ullring of the Norwegian Arctic Patrol, Royal Norwegian Navy, off Jan Mayen in the middle of the winter (1940—41), the value of 13,000 I.U. per gram liver was obtained. Biological test groups of rats were given the oil extracted from the liver in doses calculated to be equivalent to either 2.6 or 10.3 I. U. daily. Other animals were given the international standard carotene at the same level. The results obtained agreed very well with the content found by the $SbCl_3$ method.

The liver tested for toxicity in the above mentioned experiment was from the two year old female bear. Although a value of 18,000 I. U. of vitamin A per gram liver had originally been obtained, the liver portion now tested contained only 10,000 I. U. per gram. Carefully planned tests were difficult because of the reluctance of the rats to eat the liver. The same disinclination has since been observed in rats when given the livers of other rats which had been allowed to accumulate very high reserves of vitamin A. In later experiments, we repeatedly observed the unwillingness of the rats to consume livers which had a very high vitamin A content. It has previously been described in this paper how animals and birds avoid eating the liver of polar bear.

One rat ate a total of 33.1 grams of the bear liver during a period of twenty-two days, an amount containing an average of about 15,000 I. U. of vitamin A per day. It became anemic and the hind legs appeared to be paralysed. When moribund it was killed. At autopsy, the profuse internal hemorrhage typical of hypervitaminosis A was found particularly under the skin, and also in the pericardium.

Another rat ate 5.3 grams of liver during a period of nine days. It then accidentally cut a paw on the side of the cage and bled to death. On superficial examination the wound appeared too slight to have caused death in a normal animal.

A third rat ate 24 grams of liver in twenty-two days without any ill effects. Two other rats which received smaller doses were also unaffected.

Attempts to fractionate the liver into toxic and non-toxic constituents were unsuccessful. An aqueous extract of the liver, and also the residue obtained after the removal of most of the vitamin A from the liver by extraction with alcohol, was readily consumed without ill effects, in amounts corresponding to 1—2 grams of fresh liver daily. Two rats given the residue after aqueous extraction of the liver, however, also sustained no injury, although almost all the vitamin A was contained in this fraction.

In our tests with rats one animal succumbed with lesions specific for hypervitaminosis A. Other rats which ate almost as much of the liver showed no obvious sign of injury. It was, therefore, concluded that if bear liver is toxic to the rat for any reason other than its high content of vitamin A, the amount which must be eaten to cause poisoning must be so large that it renders the animal liable to concurrent hypervitaminosis A. As far as could be concluded from experiments with rats, which may of course differ widely from man in their toleration of toxic substances, there seemed no reason to look beyond vitamin A for the cause of toxicity in man; although there is good evidence for the presence of other toxic substances in the tissues of Arctic animals, which would probably be poor in vitamin A.

Rodahl and Moore (1943) also report a case of presumed poisoning through excessive halibut-liver oil consumption, which may be of interest in the present connection. One of the men engaged in the manufacture of the oil at Crooks Laboratories, took, without instruction, 4—5 oz daily. After five days, he became severely ill, the main symptom being giddiness. The ingestion of oil was then discontinued, and he rapidly recovered, returning to normal in 8—10 days. The daily dose must have been about 6,000,000 I. U.

This amount of vitamin A would be present in 300 grams of bear liver containing 20,000 I. U. of vitamin A per gram, which is not an excessive portion to be eaten in a single meal. It must be noted, however, that illness is reported to follow the ingestion of polar bear liver after one meal, while the above mentioned poisoning as a result of halibut liver oil occurred after the oil had been taken for a period of 5 days.

2. Collecting of the Material.

As a result of preliminary investigations into the reason for the toxic effect of bear and seal liver, we interpreted the symptoms that occurred in rats given bear liver, as hypervitaminosis A. A definite conclusion could not be reached, however, from these preliminary experiments, as only a small number of experimental animals were used and as the material so far only consisted of the livers of three polar bears and two bearded seals.

A closer study of the toxic effect of bear liver in experimental animals seemed therefore desirable, including further attempts to isolate the toxic substance in the bear liver. It also seemed desirable to extend the investigations to include other Arctic mammalian livers as well, such as fox, walrus and hare. Due to conditions, however, further material could not be collected, and the work had to be discontinued for the duration of the war.

I was given the opportunity of continuing the investigations as a member of the Danish airborne expedition to Pearyland, North East Greenland, in the summer of 1947, the chief purpose of which was to study the biology, geography, glaciology, and geology of the comparatively unknown areas around Brønlundsfjord, 82° 30′ N, 32° W.

During the expedition a number of livers from Arctic mammals, birds and fish were collected. This material will be subject to a later publication. In the present paper we shall only consider the livers of polar bear, Greenland fox, snow hare and walrus. The collected material was brought back to Norway and examined at the Institute of Physiology, University of Oslo, after the return of the expedition.

The livers of two polar bears were collected during the summer. Both bears were shot by Captain John Giæver in the pack ice, east of Greenland, latitude 74° N, in July 1947. The livers were removed immediately after the animals were shot and kept in saturated brine in a wooden barrel.

One of the samples (No. 52) was from an approximately five years old female polar bear (with a one year old cub). The other sample (No. 53) was also from a female polar bear approximately five years old, which had no cub, shot at the same place as the previously mentioned bear (No. 52). The total weight of the liver in both cases was approximately 5 kg.

The vitamin A content of the two bear livers was determined spectrographically in November 1947. The livers were extracted by alcohol and ether as follows (technique devised by E. Kvalheim, — personal communications):

A sample of 10.0 grams taken from the central part of the liver was ground with sand, and absolute alcohol was added in small portions

until the content of the mortar had a porridge-like consistency. Further quantities of alcohol were added during continuous stirring until a total of 25 ml. The mixture was then filtered through a glass filtering crucible. The mortar was rinsed with absolute alcohol which was filtered through the filtering crucible during stirring. The liver was further washed out by new portions of alcohol. Altogether 100 ml of absolute alcohol was used.

1. The alcohol extract was transferred to a separation funnel, the double amount of water was added (200 ml), and it was thoroughly extracted four times with ether (75—100 ml).
2. The liver substance in the filtering crucible was extracted with ether six to eight times (30—40 ml), the ether being added and thoroughly mixed by stirring with a glass rod for approximately one minute, and afterwards filtered.

The ether extracts were collected and washed twice carefully with water after which the ether was evaporated under vacuum.

When the ether and most of the alcohol had been evaporated, some water was left behind in the flask which was difficult to remove without increasing the temperature above 40° C. 10 ml of absolute alcohol was then added and the distillation under vacuum was continued until a clear light yellow oil was obtained.

For spectrographical analysis the fat was dissolved in absolute alcohol to a content of approximately 1,500 I. U. of vitamin A per 100 ml solution.

The liver of the first bear (No. 52) was found to contain 14.2 % fat, which had a potency of 154,500 I. U. vitamin A per gram, corresponding to 21,900 I. U. vitamin A per gram liver.

The liver of the second bear contained 11.3 % fat, with a potency of 236,500 I. U. vitamin A per gram, corresponding to 26,700 I. U. vitamin A per gram liver.

A sample of the oil from the second polar bear liver (No. 53) was saponified, and was then found to contain 1,107,000 I. U. of vitamin A per gram fat. The saponified fat was light yellow in colour and solidified at room temperature.

In order to investigate whether part of the vitamin A content of the bear liver was extracted by the brine and transferred into the liquid, a sample of the brine was examined. The total amount of brine in the wooden barrel containing the two bear livers (livers No. 52 and No. 53) was 1 ½—2 liters. The livers were originally placed in dry salt, so the brine consisted of blood, water and salt, as well as possible fat substances extracted from the livers.

The brine was brown in colour. It was found to contain some particles of liver.

From an average sample of the brine, 50 ml was transferred into a separation funnel and extracted several times by alcohol and ether. The ether extract was washed with water, the ether evaporated under vacuum and the total amount of fat was weighed.

50 ml of brine was found to contain 160 mg of fat, i. e. 3.2 g fat per liter brine, or in other words, approximately 4.8—6.4 g fat in the total amount of brine. This will mean that from 1 gram bear liver, approximately 0.0006 g of fat was extracted by the brine, corresponding to approximately 120 I. U. of vitamin A per gram liver, the total weight of the two livers being approximately 10 kg. The amount of vitamin A that was transferred to the brine was in other words of no practical importance (less than 0.5 %) and it may be concluded that the preservation of the liver in brine did not cause any significant loss of vitamin A from the liver to the brine.

On the other hand, it was found that the brine partly consisted of water extracted from the liver. This would mean that the figures for the vitamin A content in the salted liver would be too high compared with fresh unsalted liver.

It is evident from this that while the vitamin A content in the liver oil must be regarded as relatively unaffected by the salting, the stated figures for the vitamin A content per gram liver substance are somewhat high in the salted liver. On the other hand, a possible deterioration of the vitamin A content of the liver, as a result of four months storage (July to November) must be taken into consideration.

Oil extracted from one of the bear livers (No. 52) was found to have only a very slight antirachitic effect.

3. General Methods.

a) Arrangement and Conditions of the Experiments.

The main purpose of the experiments was to answer the following questions:

1. Is the polar bear liver toxic to experimental animals, and if so —
2. Which is the toxic substance?

In order to answer these questions and with the results of the preliminary investigations in view, it was found desirable to investigate the effect of various fractions of the polar bear livers given to rats and to compare the effect of bear liver oil with the corresponding amount of vitamin A concentrate from other sources. It was also necessary to study the effect of bear liver and bear liver oil where the vitamin A had been removed.

For these experiments young albino rats were used with initial body weights from 40 to 50 grams. In one experiment older rats with initial body weights from 70 to 80 grams were used. The rats were

taken from the main stock of animals that had been living their entire life on a sufficient basal diet.

In all thirty-six animals were used for these experiments, separated into eight groups with two to five rats in each group. Both male and female rats were used.

All rats received daily as much as they wanted of the same ordinary sufficient basal diet as had been used for the stock animals. The food had the following composition (diet I):

Oatmeal	2200 g
Coarse Indian meal	4000 »
Coarse wheat flour	3000 »
Wheat embryo	2000 »
Coarse rye flour	3000 »
Dried milk (skimmed)	4800 »
Sodium chloride	102 »
Calcium carbonate	102 »
Dried yeast	800 »
Peanut oil	500 »

In one experiment additional supply of vitamin K in the form of rotten dried fish was given in addition to the above mentioned diet (diet II).

Furthermore, all rats in these experiments received two drops of a cod liver oil mixture once a week, corresponding to 150 I. U. of vitamin A, and 100 I. U. of vitamin D per rat, regardless of other sources of vitamin A. Whole maize was given once or twice a week and ordinary bread once a week. Fresh milk and water was given every day and occasionally cabbage and carrots. Liver of pig, ox or calf was given once a week.

The rats were kept separated in special cages for each group, except for two groups where each rat was kept in its own cage, in order to record the individual food consumption. Otherwise all experimental animals lived under identical conditions.

One group of five rats was used as a control group and received ordinary sufficient basal diet.

A second group of five rats received in addition to the usual basal diet (diet I), 1 gram of bear liver (No. 53) per rat per day mixed in the diet. In order to remove as much as possible of the salt from the liver so as to make it more palatable to the rat, it was washed and thoroughly rinsed in water and boiled for five to ten minutes. It was then rinsed again and mixed in the diet. This mixture was prepared fresh daily.

A third group of five rats received in addition to the ordinary sufficient basal diet (diet I), bear liver oil extracted from the same liver as used in the previous experiment. The liver oil was given in amounts corresponding to between 15,000 and 54,000 I. U. vitamin A per rat per day. The same experiment was repeated later on with a fourth group consisting of four slightly older rats, using oil extracted from the second bear liver in amounts corresponding to approximately 20—25,000 I. U. vitamin A daily.

A fifth group consisting of five rats received in addition to the diet II, the same polar bear liver oil as given to the third group.

A sixth group of five rats received in addition to the already described basal diet, (diet I), dried fat-free bear liver (No. 53) in amounts corresponding to one gram of raw liver per rat per day. (1 gram of the raw liver had originally 26,700 I. U. of vitamin A per gram). The dried fat-free liver was mixed with the ordinary basal diet, and the mixture was given to each rat individually.

A seventh group of two rats received in addition to the ordinary basal diet (diet I), crude bear liver oil, where the vitamin A had been destroyed by long-lasting exposure to sunlight, in amounts corresponding to those given to groups 3, 4, and 5.

A final group of five rats received in addition to the usual basal diet already described (diet I), vitamin A concentrate in the form of purified whale liver oil concentrate in amounts approximately corresponding to the given doses of vitamin A in the second and third experiments. The purpose of this experiment was to compare the effect produced by bear liver oil with that of purified whale liver oil concentrate, when the two oils were given in doses containing identical amounts of vitamin A.

b) Methods.

1. *Extraction of Polar Bear Liver Oil.*

The salted bear liver was partly extracted by absolute alcohol and ether and partly by acetone in Soxhlet's apparatus.

In the first case, the liver was extracted in small portions by the same technique as described on page 24.

For the extraction by acetone the liver was rinsed in water and minced in an ordinary meat mincer and transferred into a Soxhlet's apparatus and extracted in a dark room for ten to twelve hours. The acetone was completely evaporated under vacuum.

The vitamin A potency of the extracted liver oil was determined by spectrographical method at intervals. The doses of the oil were given according to the results of these determinations.

2. *Dried Fat-Free Polar Bear Liver.*

Dried fat-free bear liver was produced in the following manner: The salted bear liver was minced and transferred into a Soxhlet's apparatus and extracted with acetone twenty-four to thirty-six hours. The fat-free liver substance was then carefully heated in order to remove the acetone. The dried liver powder was then weighed and ground in a mortar and thoroughly mixed with ordinary basal diet.

3. *Salted Polar Bear Liver No. 53.*

Salted polar bear liver was thoroughly rinsed in ordinary cold tap water and was then ground in a mortar and mixed with the ordinary basal diet. It was soon found, however, that the liver was still salt in places and it was difficult to make the rat eat the liver when it was prepared in this way. The liver was, therefore, boiled for five to ten minutes and afterwards treated in the same way as previously described. It was then found that it was more readily eaten by the rats, but the individual rats consumed the liver in varying quantities. The rats were, therefore, separated and kept in individual cages and the amount of food was weighed individually each day in order to obtain an expression of the amount of liver consumed by each rat.

4. *Dosage.*

The bear liver oil and the whale liver oil concentrate were given to the rats daily by pipets which were accurately adjusted so that the exact weight of each drop was known. In some cases it was necessary to give a relatively large amount of oil and the oil was then given to the rats by two to three drops at a time at intervals.

5. *Weighing.*

All the rats in these experiments were weighed every other day.

6. *Postmortem Examination.*

In all cases where the rats died, the organs were examined as soon after death as possible. Otherwise the rats were anesthetized by ether for a few minutes to allow blood samples to be collected from living animals for examination. Immediately afterwards the rats were killed by cutting off their heads.

It did not seem likely that this short-lasting ether anesthesia could cause degeneration of the internal organs, which were immediately removed after the death of the animals and placed in 4 % formalin. For control purposes, however, normal rats were killed without ether anesthesia, and the organs were examined and compared with normal rats

which were killed after being anesthetized with ether. No degeneration of the internal organs was found in either of these two cases.

In all cases microscopical slides were prepared from the preserved organs for histological examination. The following staining methods (B. Romeis, 1924, F. B. Mallory, 1938) were used: Hematoxylin-eosin, van Gieson, Mallory's staining, Kossa's staining, and Turnbull's staining for blood pigment. Frozen sections of some of the internal organs were stained by sudan III. In the present investigation mitrochondria staining was not used, and the applied staining methods allowed only marked degenerative changes to be recognised.

7. *Blood Examination.*

For the routine examination of the blood, samples were collected from the animal under ether anesthesia just prior to being killed, as already described. In a few cases, blood samples were collected from the rats' tails.

Hemoglobin was determined in all cases by the same Zeiss Ikon Hemoglobinometer (Standard: 13.8 g hb./100 ml blood = 100 %). Blood counts were made in the usual manner, and the sedimentation reaction was carried out by the micro method. In most cases blood smears were taken for differential counts, and in a few cases smears from the sternal marrow were prepared. For a rough determination of the coagulation time, drops of blood were placed on a glass and the time was noted when the coagulation was complete. In some cases a long Pasteur pipet was used for this purpose. In a few cases the prothrombin time was determined by Quick's method.

8. *Calcium Determination in the Rat Bones.*

The femur was removed immediately after death, cleaned and weighed. The bones were dried until a constant weight was reached at a temperature of 104° C.

After this the bone was ashed at 800° C until constant weight.

The ash was dissolved in 1-n.HCl in the porcelain vessels. The solution was transferred into measure flasks and made up to 50 ml with distilled water. A certain amount containing less than 10 mg calcium was taken out.

This was transferred into centrifuge tubes and two drops of methyl red were added. Approximately one drop of concentrated NH_3 was added (the solution must have a pH of 5). The surplus of NH_3 was neutralised by 2 % acetic acid. A surplus of saturated $(NH_4)_2C_2O_4$ was added. Water was added in the tube up to 40 ml and was left for precipitation overnight and then centrifuged and the liquid was removed. It was then washed once with 10 ml of ½ % NH_4OH. The precipitate

was stirred up with a glass rod and ½ % NH_4OH was added up to 40 ml, and it was again centrifuged, after which the solution was removed.

The precipitate was dissolved in 10 ml l-nH_2SO_4 in the centrifuge tube on a water bath at approximately 80° C.

The solution was titrated with n/10 $KMnO_4$.

9. *Urine Examination.*

At intervals urine samples were collected during a period of twenty-four hours from the various groups by placing the rats in specially constructed cages. During this period the rats received no food and were only given water in order to avoid contamination of the urine by food. The urine was collected and investigated in the ordinary way.

A dense granulated precipitation which was sometimes found on the bottom of the urine flask was examined. It was found to be sawdust which had been transferred by the rats from their respective cages. The reaction on starch gave negative result (by iodine).

To avoid contamination of the urine sample by feces, a very fine netting was placed underneath the cage, so that the feces was collected on this, while the urine was allowed to run down along the sides of the glass funnel into a flask which fitted tightly to the end of the glass funnel.

Urine samples were collected in the same manner for the determination of the excretion of calcium during twenty-four hours, in which case a few drops of toluene were added to the urine sample.

10. *Feces Examination.*

At intervals feces from the various groups were examined by the benzidine test as follows:

Fresh benzidine reagent was prepared in the usual manner. A sample of the feces was smeared out on a glass slide, one drop of the benzidine reagent was added and the time noted by stop watch.

4. Results.

a) The Toxic Effect of Polar Bear Liver on Rats.

The Control Group.

For control purposes rats of approximately the same weight as the other groups were used. They were kept under the same conditions as the other rats and received the same basal diet in unlimited quantities.

In this group, the initial average weight was 50.2 grams, varying from 47 to 53 grams. The average weight curve throughout the experiment is shown on page 32. At the end of the first ten days of the experiment the weight increase was 59.7 % of the initial weight, the

average daily weight increase being 3.0 grams. At the end of the first thirty days of the experiment the weight increase was 175 % of the initial weight, during which period the average daily weight increase was 2.9 grams.

The average daily dose of vitamin A was 20 I. U. per rat corresponding to 0.30 I. U. per gram body weight during the first ten days, and 0.20 I. U. per gram body weight during the first thirty days.

At intervals urine was collected and examined during periods of twenty-four hours, in the same manner as previously described.

At the end of the first month of the experiment the Heller's test was found to be negative, as was the benzidine test and the acetic acid test, and by microscopical examination of the centrifuged urine, no red blood cells were found.

The urine was examined again five days later and finally on the fiftieth day of the experiment with the same negative result in both cases.

Feces were collected at intervals and examined with the benzidine test, which was found to give inconsistent results with rat feces. In all cases the benzidine test was negative in this group, except for one case when it was positive after ten seconds. On this particular occasion the benzidine test was positive in feces from all the groups.

X-ray examination of the bones in rat Nos. 3 and 4 was carried out at the end of one month of the experiment. No fractures or any pathological findings were made. Rat No. 3 was again X-rayed at the end of two months of the experiment and again normal conditions were found.

Throughout the whole experiment the rats were in good condition and free of any symptoms. They were killed and examined in the same manner as the other groups and in all cases normal organs were found.

By microscopical examination of the organs no pathological findings were made in the liver, kidneys, stomach, intestines, spleen, adrenals, pancreas, testis, thyroid gland, heart, lungs or bones.

There was, however, a slight degree of hyperemia in some of the organs such as the lungs, liver and kidneys which was probably due to the ether anesthesia.

By sudan staining the usual sudanophilic zone was observed in the adrenals, while no sudanophilic substances were detected in the liver or kidneys.

The ash content of the femurs was 50.1 % calculated on a dry basis, and the average mineral content of the ashed bones was as follows: Calcium 37.5 %, phosphorous 18.3 %.

During the examination, blood smears were taken and hemoglobin and sedimentation reaction were examined. In rat No. 1 the hemoglobin was 114 %, in rat No. 3: 101 %, and in rat No. 5: 95 %. The sedimentation reaction was 10 mm in rat No. 1, and 5 mm in rat No. 5. The blood coagulated within five minutes in all rats in this group. The results of

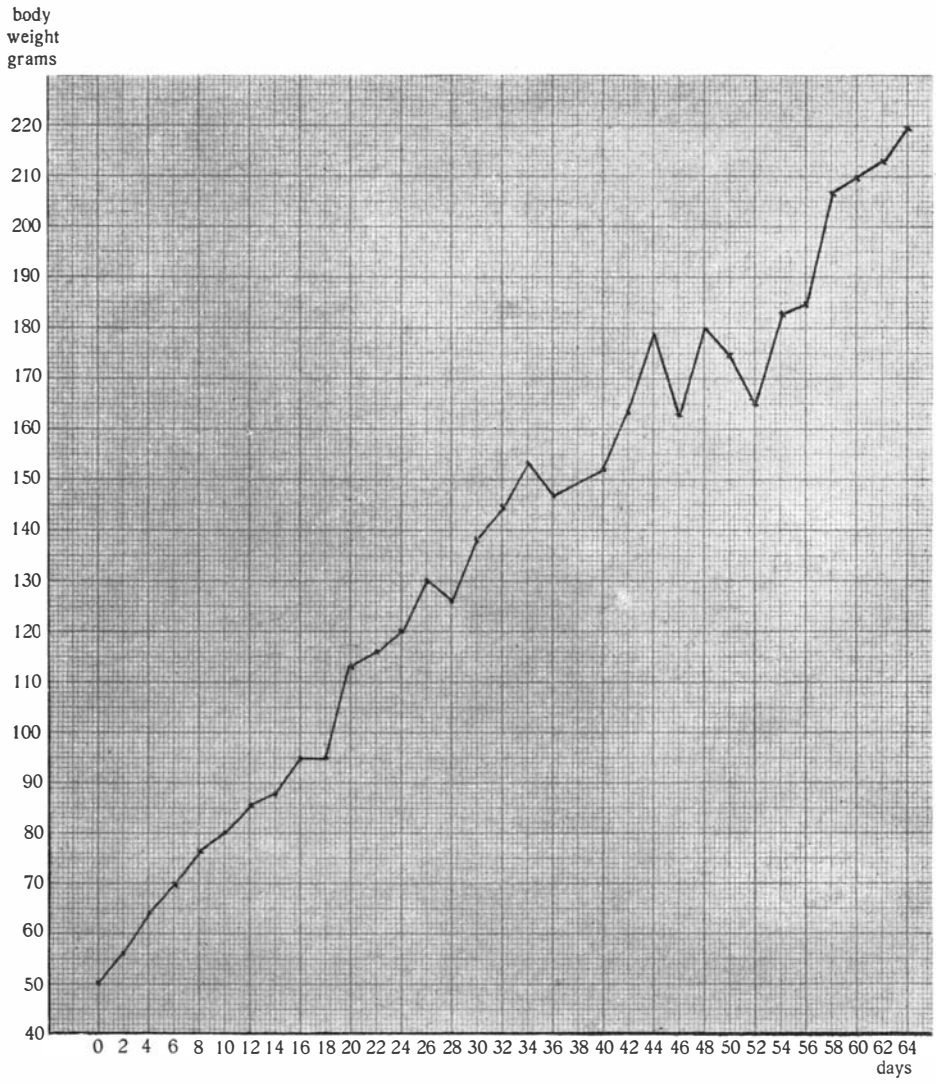

Fig. 1. Average weight curve for the controll group.

differential blood counts are shown on page 83. The calcium content was determined in the serum by Kramer-Tisdall's method and the value was found to be 11.6 mg/100 ml.

The liver from rat No. 1 was extracted by acetone in Soxhlet's apparatus 10—12 hours in a dark room and the vitamin A content was examined spectrographically in the fat. The weight of the liver was 10 g, the yield of oil was 2.1 %, and the vitamin A content was 38,600 I. U. per gram oil or 810 I. U. vitamin A per gram liver.

The Toxic Effect of Polar Bear Liver.

Salted bear liver (sample No. 53) containing 26,700 I. U. vitamin A per gram, was first given raw to five rats after having been rinsed in water, ground and thoroughly mixed with the ordinary basal diet. It was soon found, however, that the rats were reluctant to eat this liver mixture, and the liver was therefore prepared in the following manner: A weighed portion of the liver was rinsed in running water over night, boiled for five to ten minutes, and then ground in a mortar and thoroughly mixed with ordinary basal diet. This was then given to the rats in amounts corresponding to one gram of raw liver per rat per day.

During the first thirty days of the experiment the food intake was weighed daily in order to obtain an expression of the daily consumption of vitamin A per rat. During this period, the rats were kept in individual cages as the consumed amount of liver varied from rat to rat and from day to day.

Rat No. 2 was given polar bear liver (No. 53) for forty-five days. The initial weight was 45.5 grams, and at end of this period the weight was 111.2 grams. This corresponds to an average daily weight increase of 1.45 grams, which is approximately half of the weight gain in the control rats. The average daily consumption of bear liver was 0.6 grams, corresponding to a total of 28 grams during forty-five days. At the end of this period the bear liver was removed from the diet and the rat was given an ordinary sufficient basal diet for fifty days. During this period the average daily weight increase was 2.97 grams, which is approximately the same as the weight gain in the control rats.

At the end of sixteen days, rat No. 4 died after having ingested a total of 11.5 grams bear liver, corresponding to a daily average of approximately 0.7 grams.

During the same period the other rats in this group had consumed the following amounts of bear liver:

Rat No. 1	.....	8.3 grams
Rat No. 2	.....	10.5 »
Rat No. 3	.....	8.2 »
Rat No. 5	.....	7.5 »

At the end of the first thirty days of the experiment, the rats had ingested the following amounts of liver:

Rat No. 1	.....	16.3 grams
Rat No. 2	.....	19.8 »
Rat No. 3	.....	15.1 »
Rat No. 5	.....	20.3 »

The average daily consumption of bear liver for the first thirty days of the experiment was as follows:

Rat No. 1	.....	0.5 grams
Rat No. 2	.....	0.6 »
Rat No. 3	.....	0.5 »
Rat No. 4	.....	0.7 »
Rat No. 5	.....	0.6 »

During this period the average daily consumption of bear liver for all the rats in this group was 0.6 grams.

At the end of sixty-five days rat No. 1 died after a total consumption of 36 grams of bear liver, corresponding to a daily average intake of 0.5 grams.

The ingested amounts of bear liver during the whole experiment are tabulated as follows:

Table I.

Showing Amounts of Polar Bear Liver (g) Consumed per Rat During the Whole Experiment.

Rat No.	Duration of Experiment, Days	Bear Liver Consumed, Grams			
		Total	Per Day, Average	Per Day, Max.	Per Day, Min.
1	65	36	0.5	1.0	0.0
2	45	28	0.6	1.0	0.0
3	100	50	0.5	1.0	0.0
4	16	11.5	0.7	1.0	0.3
5	97	54	0.5	1.0	0.0

It is thus evident that in one of the rats 0.5 grams bear liver daily caused death after sixty-five days (after a total consumption of 36 grams bear liver). In another rat death occurred after an average daily consumption of 0.7 grams bear liver, at the end of sixteen days (after a total consumption of 11.5 grams bear liver). In the other three rats in this group a daily consumption of 0.5—0.6 g bear liver did not prove fatal.

During this experiment urine was collected for examination of the presence of protein, blood and sugar, from the fifty-third to the fifty-fourth day of the experiment, the sixty-fourth to the sixty-fifth day, and the eighty-fifth to the eighty-sixth day of the experiment.

In the first case Heller's test and the acetic acid test were faintly positive, but the benzidine test was negative. By microscopical examination of the urine after centrifugation no red blood cells were found, while a great number of crystals and Escherichia coli were seen. Haines' test for sugar was negative.

In the second case the urine was contaminated by feces. Heller's test was positive, the acetic acid test was positive, and the benzidine test was positive after ten seconds. By microscopical examination of the urine, hematuria was disclosed (several red blood cells per field of vision) and a great number of crystals were found.

In the third case, Heller's test was positive, but the benzidine test was negative.

Urine from rats Nos. 3 and 5 was collected in the course of twenty-four hours, in a specially constructed metabolism cage for the determination of calcium. The excreted amount of urine during twenty-four hour periods was approximately 2 ml per rat (varying from 0.5 to 4 ml). The secreted amount of calcium was found to be 0.1 mg per rat in twenty-four hours, as against 0.5 mg in control rats.

The benzidine test in the feces gave varied results, sometimes it was strongly positive (rats Nos. 3 and 5) after five seconds in repeated tests, while a control test in feces from normal rats gave a negative result. Other times, the benzidine test was negative. The feces had a different colour compared with the other groups, being much darker, practically blackish-green in colour (melena?).

S y m p t o m s.

The symptoms in the individual rats in this group were as follows:

R a t N o. 1. ♀. The initial weight of this rat was 45.5 grams as against 69.8 grams at the end of the experiment. The highest weight during the experiment was 100.0 grams. The rat died after sixty-five days after a total consumption of 36 g bear liver, corresponding to an average of 0.5 g per day.

The average increase of weight per day throughout the whole experiment was 0.24 grams as against approximately 3.0 grams for the control group.

During the first thirty days of the experiment the weight curve showed a slight rise, but the increase of weight was far less than the control group. The average liver consumption was 0.5 g per day varying between 0 to 1.0 g in this period. From the fourteenth to the eighteenth day a distinct fall in the weight curve was observed following an increase of the liver consumption from the tenth to the fifteenth day of the experiment.

A similar increase in the liver consumption took place from the thirtieth day, and from this date the weight curve fell steadily.

On the fifteenth day of the experiment a distinct oedema of the palpebrae was observed after a total consumption of approximately 8.3 g liver. This swelling of the palpebrae disappeared again after a few days.

Limping was observed on the right hind leg on the twentieth day, although no fracture could be detected by X-ray examination. This limping persisted approximately one week without any distinct fracture of the bone being diagnosed by X-ray examination.

On the twenty-fifth day of the experiment swelling (oedema) of the palpebrae was once more noticed, which again disappeared in the course of a few days. The oedema was in other words inconsistent.

On the forty-second day, fracture of the right hind leg was clinically diagnosed. Two days later X-ray examination revealed a distinct fracture of the right fibula.

On the forty-seventh day a severe degree of dyspnoea was noted, which developed into a persistent stridor. The weight curve was still falling.

On the fifty-sixth day a distinct oedema around the eyes was again observed as well as soreness around the mouth, and there were fractures of all four extremities. This was verified by X-ray examination.

The rat died on the sixty-fifth day of the experiment.

The rat was kept in a refrigerator over night and examined approximately twenty hours after it had died.

By postmortem examination the following pathological findings were made:

External examination: Bleeding around the medial side of the eye (the nasal canthus) where blood crusts were observed. Marked loss of hair was found around the nose and mouth, and otherwise all over the body. A moderate swelling of the tongue was observed. One of the teeth on the upper jaw was broken. Both eye balls were soft and the contents poured out by slight touching with the forceps.

Internal examination: By removal of the skin a subcutaneous collection of pus was found over a large area of the abdomen. On the neck and elsewhere on the body, large dilated subcutaneous blood vessels were found. The thorax appeared to be enlarged and relaxed. The ribs were widely separated and there was stenosis in the trachea (the rat had had stridor). The pleura cavity contained a slight amount of free blood.

There were hemorrhages in the lung tissue in patches, and pronounced emphysematous changes in the left lung. By placing pieces of the lung into water, they were found to float.

The peritoneum was slightly green in colour and was covered with a slightly green coloured slime. The liver appeared moderately enlarged.

By microscopical examination of the kidneys, marked hyperemia and considerable degeneration of the tubules was observed. In the adrenals there was marked hyperemia on the border between the cortex and the medulla. In the bones there was great irregularity of the bone structure.

Rat No. 2. ♂. The initial weight was 45.5 grams. During the first thirty days of the experiment there was a slight but even rise in the weight curve. The average daily liver consumption during this period was 0.6 g, varying between 0 to 1.0 g. After the first thirty-three days of the experiment there was a distinct fall in the weight curve. At the end of forty-five days of the experiment the bear liver was removed from the diet and a rapid and even increase of the weight followed.

On the fifteenth day, exophtalmus and oedema of the palpebrae occurred after a total consumption of 10.5 g liver.

On the seventeenth day of the experiment distinct limping was observed but in spite of this no fracture could be revealed by X-ray examination.

On the twenty-third day fractures of both hind legs were clinically certain, and were verified by X-ray examination. At this time, the condition of the rat was particularly poor. There was a marked loss of appetite so that the food consumption was negligible. Two days later a distinct swelling of the palpebrae was again observed and on the twenty-seventh day limping of the right fore leg was also seen. On the forty-fifth day there were fractures of all four extremities. These fractures were verified by X-ray examination. The bear liver was then removed from the diet.

Three days later blood crusts and small hemorrhages around the eyes and mouth were observed. This condition became worse in the course of the following couple of days, and these symptoms persisted constantly until the rat was killed.

Thirteen days after the bear liver had been removed from the diet, the left hind leg was completely healed in a wrong position (see ill. 4 and 5).

On the seventy-second day of the experiment, twenty-seven days after the removal of the bear liver, a considerable improvement in the general condition of the rat was observed, but the eye symptoms were still pronounced. In the following days, the eye symptoms became worse (see ill. 2).

On the ninety-fourth day of the experiment, X-ray examination showed that the fractures on both fore legs were also completely healed.

The rat was killed the following day, — fifty days after the polar bear liver had been removed from the diet. The hemoglobin was 88 %, red blood cells: 5.16 million per 1/1000 ml, colour index 0.8. The blood coagulated normally (within five minutes). The results of differential blood counts are given on page 83.

By postmortem examination the liver was found to be slightly patchy. The surface of the liver facing the diaphragm had a fatty and granulated appearance. Otherwise the surface was even and shiny. The suprarenal glands were small and brown-black in colour. Apart from this, no pathological findings were made by the internal examination.

Microscopical examination of the kidneys, liver, adrenals, pancreas, intestine and the tibia showed some scattered red blood cells outside the capillaries in the liver. There was hyperemia in the adrenals and kidneys, and in the latter dilated and slightly degenerated tubules were seen. The bones showed marked changes, particularly at the fractures with highly irregular bone structure.

Rat No. 3. ♂. The initial weight of the rat was 44.7 grams. When it was killed, one hundred days after the beginning of the experiment, it weighed 188 grams. During the whole experiment the increase of weight per day was 1.4 grams, that is, approximately half of the normal.

During the entire experiment the weight curve showed a slight rise with isolated peaks, but on the whole it remained much more level than the control group.

During the first thirty days of the experiment the average daily liver consumption was 0.5 g, varying between 0 and 1.0 g. The total consumption of liver throughout the whole experiment was 50 g corresponding to an average daily intake of 0.5 g.

On the fifteenth day of the experiment oedema of the palpabrae was observed after a total consumption of 8.2 g liver. Four days later limping on both hind legs was observed after a total consumption of approximately 10 g liver. This limping disappeared after a couple of days but reoccurred the forty-first day of the experiment, after the bear liver consumption had been increased to some extent. Following this increase of the liver consumption, a fall in weight was observed.

On the forty-fifth day of the experiment, swelling of the palpebrae (oedema) was again noticed. This swelling improved somewhat in the course of the following three days, but a few days later soreness of both palpebrae on both eyes was observed. On the fifty-fourth day, fractures were clinically diagnosed after a total consumption of 28.2 g liver. X-ray examination at the end of two months of the experiment revealed a fracture of both radius and ulna on the left fore leg. X-ray control the ninety-seventh day showed that these fractures were completely healed, in spite of the fact that the liver was continuously given in unchanged doses.

The rat was killed in the usual manner on the hundreth day of the experiment. The hemoglobin was 89 %, red blood cells 4.78 million per 1/1000 ml, colour index 0.95.

At autopsy no significant pathological findings were made.

Microscopical examination showed no significant pathological changes in the liver apart from some scattered red blood cells outside the capillaries.

Rat No. 4. ♂. The weight at the beginning of the experiment was 42.3 grams. The rat died after sixteen days, at which time the weight was 58 g.

Already from the commencement of this experiment it was seen that this rat had a greater appetite and ingested larger quantities of the liver than the other rats in this group.

On the tenth day of the experiment distinct limping on both hind legs was observed. On the following day, fractures on the left hind leg and left fore leg were clinically diagnosed. These were verified by X-ray examination. Simultaneously blood crusts were observed around the mouth as well as bleeding in the skin on the back. On the fifteenth day of the experiment a swelling (oedema) of both palpebrae was observed.

The weight curve showed an increase until the eleventh day of the experiment, after which it fell rapidly until the rat died on the sixteenth day of the experiment.

The average daily consumption of bear liver was approximately 0.7 g varying between 0.3 and 1.0 g, which was the largest daily liver intake observed in this group. The total consumption of liver throughout the experiment was 11.5 g.

The rat was examined immediately after death, and the following findings were made at autopsy: No signs of violence were found, nor any signs of external bleeding at the time of examination. Slight loss of hair around the mouth was observed as well as a distinct fracture of the right hind leg. There was marked oedema around the eyes on both sides, involving both papebrae superior and palpebrae inferior.

A large hemorrhage was found on the medial side of the left fore leg and in the axilla. The hemorrhage was also found to infiltrate the musculus pectoralis major. A considerable subcutaneous hemorrhage was also found around the right scapula as well as in the deeper tissue. There was a large hemorrhage around the fracture on the right hind leg where the bone protruded through the muscles. A considerable hemorrhage was also found behind the frontal neck muscles and this hemorrhage extended into the underlying tissue.

A very sharp bending of the spine was observed but no spinal fracture could be clinically diagnosed. Scattered blood extravasations were found in the pericardium. The heart was filled with coagulated blood, and some uncoagulated watery blood was found in the pleural cavity. This was possibly due to hypostasis.

There was a marked hyperemia in the abdomen. The liver was dark in colour, blood congested, and the cut surface appeared fatty. Some degree of hemorrhage was found around the kidneys.

Microscopical examination of the kidneys, liver, adrenals, spleen, intestinal tract, testis, heart, lungs and bones showed marked hyperemia in the liver, with scattered red blood cells outside the capillaries. In the

liver cells a large number of vacuoles were seen. There was marked hyperemia in the kidneys and slight degeneration of the tubules. Hyperemia was also found in the heart, stomach, bowel and small intestines. There was also degeneration of the testis. Hyperemia and hemorrhages were also found in the lungs, which showed signs of pneumonia.

Rat No. 5. ♀. The initial weight was 46.2 grams. The weight curve showed a very slight rise throughout the whole experiment, the average weight increase per day being less than one gram, which is approximately one third of the normal. The rat was killed after ninety-seven days at which time the weight was 123.5 grams.

The average daily bear liver consumption in the first thirty days of experiment was 0.6 g. In the whole experiment, the total liver consumption was 54 g with an average of 0.5 g per day, varying between 0.0 and 1.0 grams.

On the fiteenth day of the experiment oedema of the palpebrae was observed, after an ingestion of a total of 7.5 grams liver.

On the nineteenth day of the experiment limping on both hind legs was observed after a total ingestion of 9.5 g liver.

Also in this rat the oedema of the palpebrae was found to be inconsistent, occurring with long intervals.

Distinct fracture of the right fore leg was observed on the fifty-eighth day of the experiment (verified by X-ray examination), after an ingestion of 14.9 g bear liver.

X-ray examination revealed that the fracture of the right fore leg was completely healed thirty-six days after the fracture had been diagnosed.

The bear liver was removed from the diet two days before the rat was killed. The hemoglobin was 81 %, red blood cells 5.24 million per 1/1000 ml, colour index 0.77.

At autopsy the liver was found to be mottled, and the suprarenal glands had a speckled, granulated appearance. Otherwise, no pathological findings were made.

Microscopical examination of the internal organs showed hyperemia in the liver with scattered red blood cells in the liver tissue. There was also marked hyperemia in the kidneys, and free blood was found in the tubules where a hyalin-like substance was seen in some places. The bones showed irregular arrangement of the bone cells.

Summary of Results.

From this experiment it is evident that 11.5 grams bear liver consumed in the course of sixteen days proved fatal in one rat, and 36 grams during sixty-five days in another rat. Of the remaining rats one consumed 28 grams in forty-five days, one 50 grams in one hundred days, and one 54 grams in ninety-seven days without fatal results.

Table 2.

Indicating Weights and Doses in Rats Given Polar Bear Liver Mixed in Basal Diet.

Rat No.	Sex.	Duration of Experiment, Days	Initial Body Weight, g.	Weight at the End of the Experiment, g	Average Weight During the Experiment, g.	Average Increase of Body Weight per Day Throughout Experiment, g.	Vitamin A Consumption per Day — I. U./g. Body Weight		Lethal Dose of Vit. A., I. U.			
							Average	Variations	Total	Per Day, Average	Per Day per g Body Weight, Average	Per g Body Weight, Total
1.	♀	65	45.5	69.8	75 2	0.24	197	0—349	965500	14800	197	12800
2.	♂	45[1]	45 5	111.2	82.4	1.45	199	0—436	-	-	-	-
3.	♂	100	44.7	188.2	118.6	1.45	112	0—242	-	-	-	-
4.	♂	16	42.5	58.4	58.8	1.04	325	190—445	305800	19100	325	5200
5	♀	97	46.2	123.5	98.8	0.97	152	0—267	-	-	-	-
Mean ..		(64)	44.8	110.2	95.5	1.04	155.6	—	-	-	-	-

[1] At the end of 45 days the bear liver was removed from the diet in rat No. 2, and ordinary sufficient basal diet was given during a period of 51 days. During the latter period it was found that the rat gained weight normally, — the average daily weight increase being 2.97 g (as against 1 45 g when the rat received 1 g bear liver mixed in the diet). The actual weight gain during these 51 days was from 111.2 g to 269.9 g.

It is further evident from this experiment that the clinical syptoms observed in all the rats given bear liver resembled the symptoms typical for hypervitaminosis A, such as reduced weight increase, hemorrhages, fractures etc. observed in rats receiving excess of purified vitamin A concentrates (see pages 62—69).

In the case when 11.5 grams bear liver proved lethal in the course of sixteen days, the average daily vitamin A consumption per gram body weight was 325 I. U., and in the case where 36 grams bear liver proved lethal at the end of sixty-five days, the vitamin A consumption corresponded to 197 I. U. vitamin A/g body weight daily.

Of the other clinical symptoms, eye symptoms, limping and fractures occurred in all rats, soreness around the mouth in three and alopecia in two of the five rats receiving bear liver. The first manifestation of these symptoms in relation to the time from the beginning of the experiment and the vitamin A dose in this group is given in table 3, page 43. From this table it is evident that of these symptoms, limping occurred as an average about the fourteenth day after a total consumption of approximately 210,000 I. U. vitamin A, and eye symptoms after fourteen days, after a total consumption of approximately 235,000 I. U. vitamin A. Fractures occurred in this group after an average of about thirty-seven days, after a total consumption of approximately 560,000 I. U. vitamin A. Soreness around the mouth occurred at the end of ten to fifty-five days, after a total consumption of approximately 190,000 to 800,000 I. U. vitamin A, and alopecia occurred at the end of sixteen and sixty-five days after a total consumption of approximately 300,000 and 960,000 I. U. vitamin A.

After forty-five days the bear liver was removed from the diet in one of the rats, and a marked rise in the weight curve was observed. Nevertheless eye symptoms with blood crusts and small hemorrhages around the eyes and mouth persisted until the rat was killed fifty days after the bear liver was removed from the diet.

In the urine the Heller's test and the acetic acid test were found to be positive, and red blood cells were found in the urine after two months of the experiment. In the feces, the benzidine test was positive.

The hemoglobin was determined in three of the rats and found to be 88, 89, and 81 %, the colour index being 0.8, 1.0, and 0.8 respectively. The blood coagulated within 5 minutes. Differential blood counts revealed no pathological changes.

By postmortem examination no significant pathological findings were made in three of the rats. In the other two rats subcutaneous and visceral hemorrhages were found as well as hyperemia. In one case a sharp bending of the spine was observed, and in one case the teeth appeared brittle.

The average weight curve for this group compared with the control group is given on page 44. From this it will be observed that a reduction in the normal weight increase is one of the earliest and most constant symptoms in the rats receiving bear liver.

The calcium content was determined in the serum by Kramer-Tisdall's method in two of the rats and the average value was found to be 9.9 mg/100 ml as against 11.6 mg/100 ml for the control group.

The vitamin A reserve was determined in the liver of one of the rats in this group by the technique described on page 32. The yield of oil was 4.9 %, and the vitamin A content was 175,000 I. U. per gram oil corresponding to 8,500 I. U. per gram liver, or 21,000 I. U. in the whole organ.

The average ash content of the femurs was 51.8 %, calculated on a dry basis, as against 50.1 % for the control group. The average calcium content of the ashed bones was 33.6 % (as against 37.5 % for the control group), and the average phosphorous content was 18.6 % (as against 18.3 % for the control group). Thus there appears to be no significant changes in the mineral content of the bones in the rats receiving bear liver compared with the control group.

From these observations it may be concluded that bear liver is toxic to rats in amounts corresponding to approximately 0.5 g bear liver daily.

In the following experiments the effect of the various fractions of the bear liver on rats is examined, in an attempt to isolate the toxic factor.

Table 3.

The First Manifestation of Clinical Symptoms in Relation to Time From the Beginning of the Experiment and Vitamin A Dose in Rats Given Polar Bear Liver Mixed in Basal Diet.

Symptom	No. of days from beginning of experiment until first manifestation of clinical symptoms					Total consumption of vitamin A (I. U.) from beginning of experiment until first manifestation of clinical symptom				
	Rat No 1	Rat No. 2	Rat No. 3	Rat No. 4	Rat No 5	Rat No. 1	Rat No. 2	Rat No. 3	Rat No 4	Rat No. 5
Reduced weight increase.	6	16	16	12	12	87000	307000	246000	260000	181000
Limping	19	6	18	9	18	276000	103000	260000	171000	243000
Eye symptoms	14	14	14	14	14	210000	281000	207000	276000	203000
Alopecia	65	-	-	16	-	965000	-	-	305000	-
Soreness around mouth..	55	47	-	10	-	805000	768000	-	191000	-
Fracture	41	22	53	10	57	581000	368000	738000	191000	943000
Death	65	-	-	16	-	965000	-	-	305000	-

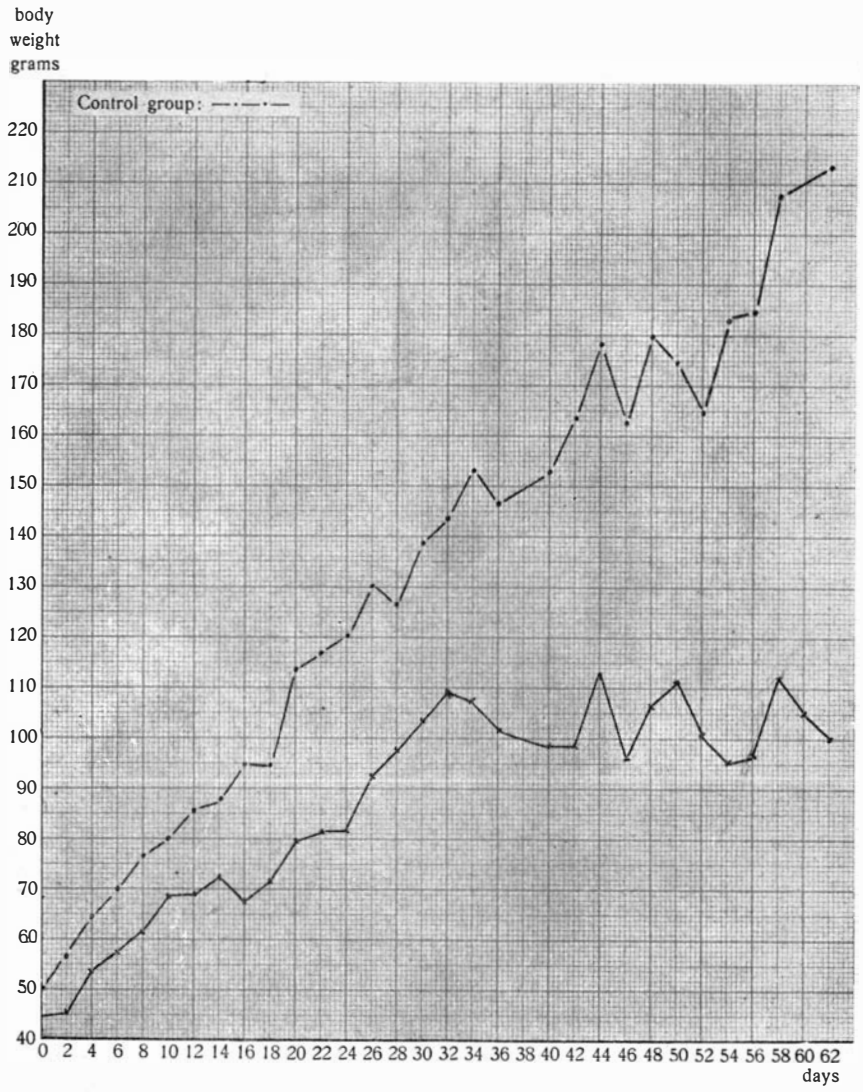

Fig. 2. Average weight curve for rats given polar cear liver mixed in basal diet compared with average weigt curve for control group.

b) The Toxic Effect of Polar Bear Liver Oil on Rats.

Experiment 1.

The purpose of this experiment was to examine the effect on rats of polar bear liver oil, — the fraction containing all the vitamin A as it was shown in the previous experiment that the symptoms produced by bear liver resembled those produced by excess of vitamin A. The bear liver was extracted with ether and alcohol or with acetone in Soxhlet's apparatus from polar bear liver No. 53. The technique for the extraction is described on pages 24 and 27.

At certain intervals the potency of the oil was examined by spectrographical determination of vitamin A, as the prepared extracts of the

liver did not always have exactly the same vitamin A potency after each extraction. The vitamin A potency of the oil varied between 150,000 to 230,000 I. U. per gram according to the technique applied.

In this experiment five rats of approximately the same weight as the rats in the other groups were used. They were given the same sufficient basal diet in unlimited quantities and except for the bear liver oil the conditions of the experiment were identical with the control group.

D o s a g e.

The bear liver oil was given by pipet to the rats in varying amounts from 20,000 I. U. up to 54,000 I. U. vitamin A per rat per day. The oil was given in two to three drops at a time but in spite of this it was impossible to make the rat swallow the total quantity, so that the figures stated for the vitamin dose must be regarded as maximum figures.

During the first forty days of the experiment less than 27,600 I. U. vitamin A per rat was given as a daily average. During the whole period of the experiment the average daily dose of vitamin A was less than 30,000 I. U. per rat.

It is likely that these figures are somewhat too high as it was shown later that the oil lost a considerable amount of its vitamin content during storage in rooms or in refrigerator temperature.

S y m p t o m s.

Shortly after the commencement of the experiment the rats looked miserable and showed signs of being in poor condition. Changes in the pelts could be seen in all rats two days after the beginning of the experiment. They were noticeably less active and appeared drowsy and weak. The muscular tonus appeared to be much less than in the control animals, and this symptom became pronounced on the sixth day.

On the sixth day of the experiment rat No. 1 limped on the right fore leg and on the seventh day a distinct stiffness of the limbs was observed in all the rats in this group.

On the ninth day, alopecia was seen to a marked extent as well as soreness around the mouth, after a total consumption of 163,000 I. U. vitamin A, corresponding to an average of 18,000 I. U. per day, or 357 I. U. per gram body weight.

On the eleventh day of the experiment rats Nos. 1, 3 and 4 limped, and rat No. 5 showed fracture by clinical examination, which was verified by X-ray examination.

The following day all the rats showed characteristic eye symptoms; exophtalmus, loss of hair, and soreness around the eyes, as well as swelling of the palpebrae (oedema). The total consumption of vitamin A was then 265,000 I. U. per rat.

The described eye symptoms persisted for several days in the surviving rats, but disappeared and reappeared again later on at irregular intervals.

At the end of thirteen days after the beginning of the experiment, rats Nos. 2, 4, and 5 died, after a total consumption of approximately 265,000 I. U. vitamin A per rat, corresponding to an average daily consumption of approximately 22,000 I. U. vitamin A. The average daily vitamin A consumption per gram body weight was as follows:

Rats No. 2 & 4	384	I. U. vitamin A/g body weight
Rat No. 5.....	428	—»—

The total dose of vitamin A per gram body weight was in these cases:

Rat No. 2	4,600	I. U. vitamin A/g body weight
Rat No. 4	4,600	—»—
Rat No. 5	5,100	—»—

Towards the end of the experiment an increase in the weight occurred in rats Nos. 1 and 3. This was probably due to the fact that the rats had learnt to avoid swallowing the oil in the course of the experiment.

During the first ten days of the experiment the average weight increase in this group was 15.5 grams (30.3 % of the initial weight) corresponding to 1.5 grams per day per rat, which is only half of the normal. The average daily weight increase during the first twelve days of the experiment was 0.3 grams.

On the fifteenth day the oedema of the palpebrae in rats Nos. 1 and 3 was very pronounced, both eyes being practically closed. On the following day the general condition of these rats was particularly poor. On the twenty-second day alopecia was observed over the abdomen of rat No. 3. In the course of a couple of days, the general condition improved to some extent while the eye symptoms occurred at irregular intervals.

On the fifty-sixth day of the experiment, rat No. 1 was very weak. Two days later a swelling of the forehead was observed, which was understood to be a periosteal hemorrhage with the formation of a hematoma.

At the end of sixty-nine days the bear liver oil was removed from the diet, and the remaining two rats (Nos. 1 and 3) were given only basal diet for a period of ten days, at the end of which time the rats were killed and examined.

By examination of the blood in rat No. 1 just prior to being killed the hemoglobin was found to be 100 %, and the sedimentation reaction was 2—3 mm. The blood coagulated within five minutes.

Postmortem findings.

At autopsy the following findings were made:

Rat No. 1. ♂. There was a fair amount of subcutaneous fat. The urinary bladder, which was full of urine, was carefully punctured with a thin needle attached to a syringe, and a sample of urine was collected, in which Heller's test was positive. The benzidine test in the feces was, however, negative. No pathologico-anatomical findings of any significance were detected.

Rat No. 2. ♂. Loss of hair around the mouth, on the neck and also on the abdomen and soreness with blood crusts around the mouth were found. There were subcutaneous hemorrhages around both shoulder blades particularly the right one. Small hemorrhages were also found in the muscles of the hind legs. The intestines and the peritoneum were partly covered by a thin slime. Hyperemia was found in the abdominal organs.

The liver was very dark in colour and blood congested. The central part of the liver had a lighter colour, but was darker in the periphery, where it was more congested.

By microscopical examination of the kidneys, liver, adrenals, spleen, intestinal tract, testis and lungs some degree of hyperemia with scattered red blood cells in the liver tissue were detected. There were signs of pneumonia in the lungs with congestion of the lung tissue and in some places the solidified lung tissue was filled with red blood cells and leucocytes. In the small intestine and the stomach there was oedema and some hemorrhage in the villi. In the kidneys some red blood cells were seen along the tubules outside the capillaries.

Rat No. 3. ♂. A fair amount of subcutaneous and visceral fat was seen, and the organs were blood congested. The suprarenal glands appeared moderately enlarged. The benzidine reaction in feces was positive.

Rat No. 4. ♀. Loss of hair was found over large areas of the abdomen and around the mouth. There was subcutaneous bleeding under both scapulae and also at the back.

A green coloured slime covered the intestine and the peritoneum. The spleen was large and very dark in colour. There were large gatherings of blood in the pleural cavity and coagulated blood in the pericardium.

By microscopical examination of the lungs, heart, kidneys, liver, adrenals, spleen and the intestinal tract hyperemia and atelectasis was found in the lungs. In the stomach there was degeneration and necrosis

in patches of the surface epithelium. In the liver there was marked hyperemia. There were also signs of slight degeneration of the liver parenchyma. In the kidneys hyperemia was found as well as slight hemorrhages in some places. There were also slight signs of degeneration of some of the tubules, while the glomeruli appeared normal. Marked hyperemia was also found in the adrenals, both in the cortex and the medulla.

Rat No. 5. ♀. It was found that the rat had suffered from diarrhea.

Marked loss of hair around the mouth, on the neck and over large areas of the abdomen was found as well as soreness and formation of blood crusts around the mouth.

There were subcutaneous hemorrhages around both ankle joints, and on both sides of the neck. Hemorrhages were also found above the upper opening of the thorax which extended up the neck.

No pathological findings were made in the abdomen.

Microscopical examination of the organs revealed similar changes as described for rats Nos. 2 and 4 in the lungs and intestines. Hyperemia was seen in the heart, liver and in the pancreas. In the kidneys, there was hyperemia, particularly in the subcortical zone. There was slight degeneration of the tubules, and some of them were filled with free blood. By Mallory-staining of the kidney, no abnormalities were detected, except for red blood cells in the space of Bowman's capsule. The adrenals showed hyperemia.

Experiment 2.

The same experiment was repeated later on with four older rats, with initial body weights from 67 to 86 grams, using oil extracted from the second polar bear liver (No. 52), in amounts corresponding to approximately 20—25,000 I. U. vitamin A daily to each rat, given by dropping pipet. The average daily dose of vitamin A per gram body weight was approximately 160 I. U. The average daily weight increase was 0.8 g during the first ten days, and 1.9 g during the first thirty days of the experiment.

The experiment lasted from thirty-seven to forty-five days. The rats in this group all developed symptoms similar to those in the previous experiment, but the doses given proved in no case lethal, — nor did any of these rats develop fractures during the time of observation, while X-ray examination revealed bone changes as observed in younger hypervitaminotic rats.

The benzidine test in the feces was positive after 10 seconds. In the urine the Heller's test was positive, and by microscopical examination of the centrifuged urine pronounced hematuria was detected.

By examination of the blood the following findings were made: The hemoglobin was 91 % (78—104), red blood cells 5.37 millions per 1/1000 ml, colour index 0.9. The prothrombin time and fasting blood sugar was determined in two of the rats, and found to be 15 seconds and 83 mg/100 ml respectively.

The blood coagulated normally. The differential blood count was practically identical with that of the normal control rats.

By postmortem examination similar findings were made as described in the previous experiment. In two of the cases auxiliary suprarenal glands were found (verified by microscopical examination). Two of the rats were females, and they were both pregnant.

Microscopical examination in one of the rats revealed similar changes in the internal organs as found in the other hypervitaminotic rats, such as hyperemia, slight degeneration of the renal tubules, and scattered small hemorrhages in the kidneys and liver. By sudan staining large deposits of sudanophil droplets were found in the adrenal cortex and in the liver, while no sudanophil droplets were seen in the kidneys.

The average ash content of the femur was 55.9 % determined on a dry basis (as against 53.0 % in control rats of the same age), and the calcium and phosphorous content of the ash was 35.7 % and 18.7 % respectively (as against 31.8 % and 17.9 % for control rats of approximately the same age).

Experiment 3.

The conditions of this experiment were identical to those of experiments 1 and 2, with the exception that in this experiment basal diet II (see page 26) was given instead of basal diet I.

The initial average weight of this group was 54.7 grams. At the end of the first ten days of the experiment the weight increase was 11.1 grams, or 20.2 % of the initial weight, as against 30.4 % in the control group. This corresponds to a daily weight increase of 1.1 grams per rat, as against 3.0 g for the control group.

The average daily dose of vitamin A during the first ten days of the experiment was 18,000 I. U., corresponding to approximately 300 I. U. of vitamin A per gram body weight. It was found that the increase of weight was reduced to one third of the normal by this dose.

At the end of the first thirty days of the experiment the average increase of weight was 52.2 grams or 95.4 % of the initial weight, as against 175 % for the control group. This corresponds to an average daily weight increase of 1.7 grams as against 2.93 for the control group.

The average daily dose of vitamin A for this period was 26,400 I. U. corresponding to approximately 362 I. U. of vitamin A per gram body weight. It was found that this dose of vitamin A reduced the increase of weight by approximately 50 % of the normal during the first thirty days of the experiment.

Urine samples were collected during twenty-four hours from the twenty-second to the twenty-third day of the experiment. Heller's test was strongly positive but the benzidine test was negative. The urine was again collected and examined from the thirty-fourth to the thirty-fifth day, — the Heller's test as well as the acetic acid test were strongly positive and by microscopical examination red blood cells were found (more than 4 red blood cells per field of vision).

Symptoms.

Every day the rats were clinically examined and the symptoms observed were as follows:

On the second day of the experiment, the rats in this group looked miserable. They showed decreased activity, and appeared to be weaker than the control animals. The pelt looked thin and untidy. On the sixth day of the experiment the appeared weak with stiffness in the legs which was understood to be caused by pains in the limbs. The unhealthy appearance of the pelt increased with loss of hair as the days went by.

On the ninth day of the experiment, after a total consumption of 130,500 I. U. vitamin A, corresponding to an average of approximately 14,500 I. U. per day, or approximately 242 I. U. per gram body weight per day, it was found that the rats had a slight degree of exophtalmus with swelling or oedema of the palpebrae. These initial symptoms were present in all rats in this group.

Rat No. 1. ♂. Following these initial symptoms, bleeding around, and particularly at the corners of the mouth, was seen, and there was a slight limping of the right fore leg on the ninth day of the experiment. Epilation was seen on the back. Around the eyes a red line was seen where the loss of hair was marked, and this was most pronounced on the nasal side of the eye.

On the eleventh day of the experiment, the limping of the right fore leg was definate. On the fifteenth day the rat suffered from diarrhea, and a distinct swelling of both palpebrae was seen. On the nineteenth day limping of the hind legs occurred. Two days later this limping was more distinct on the left hind leg, but disappeared in the course of two days, and by X-ray examination no fractures could be revealed.

The thirty-sixth day of the experiment, certain fracture of the left hind leg was clinically diagnosed, and on the forty-fourth day fracture was also diagnosed on the right hind leg. These were verified by X-ray examination.

Forty-eight days after the beginning of the experiment the rat was killed and examined. The total consumption of vitamin A was then 1,350,000 I. U. corresponding to an average daily vitamin A intake of 28,100 I. U. or approximately 350 I. U. per gram body weight. The

sedimentation reaction was 3 mm after one hour. The hemoglobin was 88 %.

No significant pathological findings were made during the post-mortem examination.

By microscopical examination the following findings were made:

Liver: Marked hyperemia and scattered red blood cells outside the capillaries. In one place a more profuse hemorrhage which had separated the liver cells.

Kidney: Marked hyperemia throughout the whole organ and particularly in the subcortical one. The capsule and the glomeruli appeared normal while free blood was seen in the space of Bowman's capsule. Some of the tubules were filled with amorphous masses, and a calcium-like substance. By Mallory-staining red blood cells were seen outside the capillaries, but no abnormalities were detected in the capillary wall, when compared with the normal control. By Turnbull-staining, signs of old hemorrhages were detected.

Stomach: No pathological findings.

Intestines: No pathological findings.

Adrenals: Marked hyperemia in the central parts of the cortex.

Thyroid: No pathological findings.

Heart: Hyperemia.

Lungs: Marked hyperemia and free blood in some of the alveoli, and thickening of the alveolar wall.

Bones: Small scattered periostal and sub-periostal hemorrhages, normal density of bone cells, large Howship's lacunae filled with necrotic cells and red blood cells.

Rat No. 2. ♂. Following the initial symptoms bleeding in the corners of the mouth was found on the tenth day of the experiment together with loss of hair and swelling of the palpebrae (oedema). At the same time a slight limping was seen on both fore legs, particularly the left.

The rat died after eleven days of the experiment, after a total consumption of 183,000 I. U. vitamin A, corresponding to 18,300 I. U. per day, or an average of 274 I. U. vitamin A per gram body weight. The entire dose of vitamin A during the whole experiment was 2,700 I. U., per gram body weight.

The average daily weight increase during the whole experiment was 1.0 grams. The increase of weight during the first ten days corresponded to 10.1 grams, or 17.3 % of the initial weight.

X-ray examination revealed a possible disunion of the epiphysis of both tibiae without this being previously detected by clinical examination.

At autopsy subcutaneous hemorrhage was seen on both sides of the neck, extending upwards towards the head. Small bleedings in patches

elsewhere were also seen. The blood looked thin as it sometimes does after death has occurred. The subcutaneous fat layer was very sparingly dispersed. Examination of the heart revealed nothing abnormal. Otherwise no pathological findings were made by macroscopical postmortem examination which could be taken as the cause for the death.

By microscopical examination the following findings were made:

Liver: Marked hyperemia and scattered red blood cells outside the capillaries.

Kidney: Marked hyperemia of the whole organ, but mostly in the subcortical zone. The glomeruli appeared normal but there was slight degeneration of the tubules.

Small intestines: Hyperemia with scattered hemorrhages and some degeneration of the surface epithelial coating.

Spleen: Blood congested.

Adrenals: Some degree of hyperemia.

Heart: Marked hyperemia.

Lungs: Hyperemia.

Testis: No significant pathological findings.

Rat No. 3. ♂. Following the initial symptoms distinct limping of the left hind leg was seen on the tenth day of the experiment. Five days later oedema of the palpebrae occurred as well as diarrhea. It was usually found that the feces was normal in the groups receiving comparatively large doses of vitamin A, and diarrhea only occurred very seldom in these experiments.

On the nineteenth day of the experiment, limping of the right hind leg was observed, and X-ray examination two days later revealed a distinct fracture of both tibia and fibula.

The rat was killed on the twenty-fourth day of the experiment after a total consumption of 608,900 I. U. vitamin A.

Marked loss of hair was found on the abdomen. There was a large hemorrhage (hematoma) around the fracture on the right hind leg, and also between the muscles around the fracture. Hemorrhages of varying sizes were found in the groin and in the armpits. All subcutaneous blood vessels were large and filled with blood. No bleeding was found in the muscles apart from around the described fracture.

The kidneys were large and dark in colour. Examination of the heart revealed possible small pericardial hemorrhages, otherwise there were no pathological findings.

By microscopical examination the following findings were made:

Liver: Hyperemia and a large number of vacuoles. By sudan III staining, sudanophil droplets were detected both in, and particularly between the liver cells (Kupffer cells).

Kidney: Hyperemia particularly in the subcortical zone. There was slight degeneration of the tubules, while the glomeruli appeared normal.

No fatty degeneration was detected in the organ by staining with sudan III.

Adrenals: The cortical cells in the zona fasciculata appeared irregularly arranged, and contained a great number of vacuoles.

Heart: Hyperemia. Large gathering of red blood cells in one place under the pericardium.

Lungs: Hyperemia and thickened alveolar walls.

Bone and muscles: Large hemorrhage in the muscle with necrotic muscle cells, replaced by connective tissue rich in cells. Marked subperiostal hemorrhages. Great irregularity of bone structure.

Teeth: Deposits of calcium in the pulp.

By Kossa's staining no deposits of calcium were detected in the kidneys, adrenals or liver.

No significant pathological findings were made in the pancreas, spleen, intestinal tract or in the testis.

Rat No. 4. ♀. Following initial symptoms the rat looked particularly run down, miserable and weak, and showed distinct signs of pains in the legs on the seventh day of the experiment. Two days later, limping was seen on the left hind leg and also on the right fore leg, after a total consumption of 130,500 I. U. vitamin A, corresponding to an average of 14,500 I. U. daily or 242 I. U. vitamin A per gram body weight.

After fourteen days of the experiment, the condition of the rat was particularly poor, it had diarrhea and swelling of the palpebrae. By X-ray examination no fracture could be verified, and only after twenty-two days a definite fracture of the left fore leg could be revealed by X-ray examination after a total consumption of 608,900 I. U. vitamin A, corresponding to an average daily dose of 27,600 I. U., or approximately 425 I. U. of vitamin A per gram body weight.

After thirty-six days of the experiment, fractures on both hind legs were also diagnosed and verified by X-ray examination, after a total consumption of 1,076,000 I. U. vitamin A, corresponding to an approximate average of 29,000 I. U. per day, or approximately 430 I. U. per gram body weight daily.

The rat was killed and examined the following day.

At autopsy it was found that the thyroid and the parathyroid glands appeared moderately enlarged. By examination of the heart, distinct hemorrhages were found in several places of the pericardium. The suprarenal glands appeared moderately enlarged.

By microscopical examination the following findings were made:

Liver: Slight hyperemia.

Kidney: Marked hyperemia, particularly in the subcortical zone. Some red blood cells were seen in some of the tubular lumen. Slight degeneration of tubules. The glomeruli appeared normal.

Heart: Hyperemia.

Lungs: Hyperemia. Thickened alveolar wall.

No significant pathological findings were revealed in the spleen, pancreas or the intestinal tract.

Rat No. 5. ♀. Following the initial symptoms possible fractures of the left fore leg and possibly also the right fore leg were clinically diagnosed after nine days of the experiment, although X-ray examination revealed no distinct fracture. At this time, a total of 130,500 I. U. vitamin A had been consumed, corresponding to an average of 14,500 I. U. daily, or 279 I. U. of vitamin A per gram body weight.

After fourteen days of the experiment the condition of the rat was particularly poor. It was very weak, had diarrhea, and swelling of the palpebrae was seen.

Ten days later limping could no longer be observed. Epilation was found in varying degrees of the palpebrae, as well as exophtalmus. These symptoms were inconsistent.

The rat was killed and examined at the end of the thirty-seventh day of the experiment. The hemoglobin was 77 %. The sedimentation reaction was 1 to 2 mm. The blood coagulated normally.

The liver was found to be speckled but the surface was even and shiny. It was very full of blood and small points of bleeding could be seen on the surface. The spleen was of normal size, rather dark and granulated.

The thymus gland was enlarged and a large fibroma was found attached to it. This fibroma was larger than the heart and was situated in the right thorax cavity.

Summary of Results.

In Experiment I all rats showed signs of being in poor condition two days after the beginning of the experiment, with changes in the pelts, decreased activity, and appeared drowsy and weak. Some days later pronounced decreased muscular tonus, stiffness of the limbs, alopecia, soreness around the mouth and eye symptoms occurred in all rats, and fractures in one. One of the rats suffered from diarrhea. During the first ten days of the experiment the average daily weight increase was approximately half of the normal.

In two cases a daily dose of 384 I. U. vitamin A per gram body weight, and in one case 428 I. U./g proved fatal at the end of 13 days, the total consumption in all three cases being 265,000 I. U. vitamin A.

By postmortem examination of the rats that died, hemorrhage and marked alopecia was found in all cases. In two cases soreness and blood

crusts around the mouth as well as signs of peritonitis were observed. In one case hyperemia was seen, and in one of the surviving rats comparatively large suprarenal glands were found.

In urine examined from one rat the Heller's test was positive, while the benzidine test in the feces was negative.

Hemoglobin was determined in one case, and found to be 100 %, the sedimentation reaction being 2—3 mm. The blood coagulated normally.

The average calcium content of the ashed femur was 35.3 %, as against 37.5 % for the control group.

The first manifestation of clinical symptoms in relation to the time from the beginning of the experiment and the vitamin A dose in the individual rats in this group is given in table 4.

From this table it is evident that some of the symptoms appeared early, taking the form of some sort of acute intoxication, while other symptoms such as limping, alopecia, fractures and eye symptoms manifested themselves after the excess of vitamin A had been given for some time.

The average weight curve for this group compared with the control groups is given on page 56.

In Experiment 3 all rats showed signs of being in poor condition on the second day of the experiment. They showed decreased activity, appeared weak and the pelts looked thin and untidy.

Table 4.

The First Manifestation of Clinical Symptoms in Relation to Time from the Beginning of the Experiment and Vitamin A Dose in Rats Dosed with Polar Bear Liver Oil. Experiment I.

Symptom	No. of days from beginning of experiment until first manifestation of clinical symptoms					Total consumption of vitamin A. (I. U.) from beginning of experiment until first manifestation of clinical symptoms				
	Rat No. 1	Rat No. 2	Rat No. 3	Rat No. 4	Rat No. 5	Rat No. 1	Rat No. 2	Rat No. 3	Rat No. 4	Rat No. 5
Poor condition	2	2	2	2	2	32000	32000	32000	32000	32000
Changes in pelts	2	2	2	2	2	32000	32000	32000	32000	32000
Decreased activity	2	2	2	2	2	32000	32000	32000	32000	32000
Drowsiness	2	2	2	2	2	32000	32000	32000	32000	32000
Weakness	2	2	2	2	2	32000	32000	32000	32000	32000
Reduced weight increase.	4	4	4	4	4	73000	73000	73000	73000	73000
Limping	5	-	11	11	-	88000	-	228000	228000	-
Stiffness in limbs	7	7	7	7	7	128000	128000	128000	128000	128000
Alopecia	9	9	9	9	9	163000	163000	163000	163000	163000
Soreness around mouth .	9	9	9	9	9	163000	163000	163000	163000	163000
Fracture	-	-	-	-	11	-	-	-	-	228000
Eye symptoms	12	12	12	12	12	265000	265000	265000	265000	265000
Death	-	13	-	13	13	-	289000	-	289000	289000

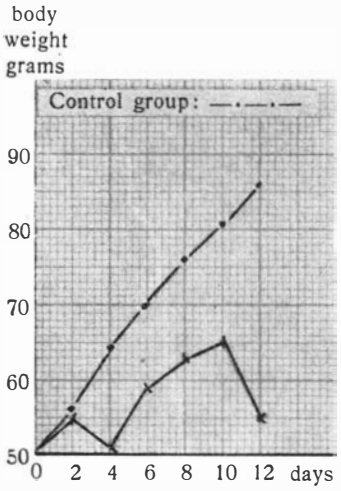

Fig. 3. Average weiget curve for rats dosed with plar bear liver oil compared with the controls. Experiment I.

Some days later symptoms indicating pains in the limbs occurred, and alopecia was observed, as well as eye symptoms. Limping occurred in all rats in this group, and fractures in four out of the five rats. Soreness and bleeding around the mouth occurred in two of the rats. Four rats suffered from diarrhea after thirteen to fourteen days.

One rat died at the end of eleven days having consumed a total of 183,000 I. U. vitamin A or 274 I. U. per gram body weight daily. By

Table 5.

The First Manifestation of Clinical Symptoms in Relation to Time from the Beginning of the Experiment and Vitamin A Dose in Rats Receiving Polar Bear Liver Oil. Experiment 3.

Symptom	No. of days from beginning of experiment until first manifestation of clinical symptoms					Total consumption of vitamin A. (I. U.) from beginning of experiment until first manifestation of clinical symptoms				
	Rat No. 1	Rat No. 2	Rat No. 3	Rat No. 4	Rat No. 5	Rat No. 1	Rat No. 2	Rat No. 3	Rat No. 4	Rat No. 5
Poor Condition	1	1	1	1	1	16000	16000	16000	16000	16000
Changes in pelts	1	1	1	1	1	16000	16000	16000	16000	16000
Decreased activity	1	1	1	1	1	16000	16000	16000	16000	16000
Drowsiness	1	1	1	1	1	16000	16000	16000	16000	16000
Reduced weight increase	2	2	2	2	2	32000	32000	32000	32000	32000
Limping	9	9	9	8	8	150000	150000	150000	130000	130000
Stiffness in limbs	5	5	5	5	5	88000	88000	88000	88000	88000
Alopecia	8	9	5	5	5	130000	150000	88000	88000	88000
Soreness around mouth	8	9	-	-	-	130000	150000	-	-	-
Eye symptoms	8	8	8	8	8	130000	130000	130000	130000	130000
Diarrhea	14	-	14	13	13	308800	-	308800	276300	276300
Fracture	35	9	18	22	-	1008000	150000	446000	576000	-
Death	-	11	-	-	-	-	215000	-	-	-

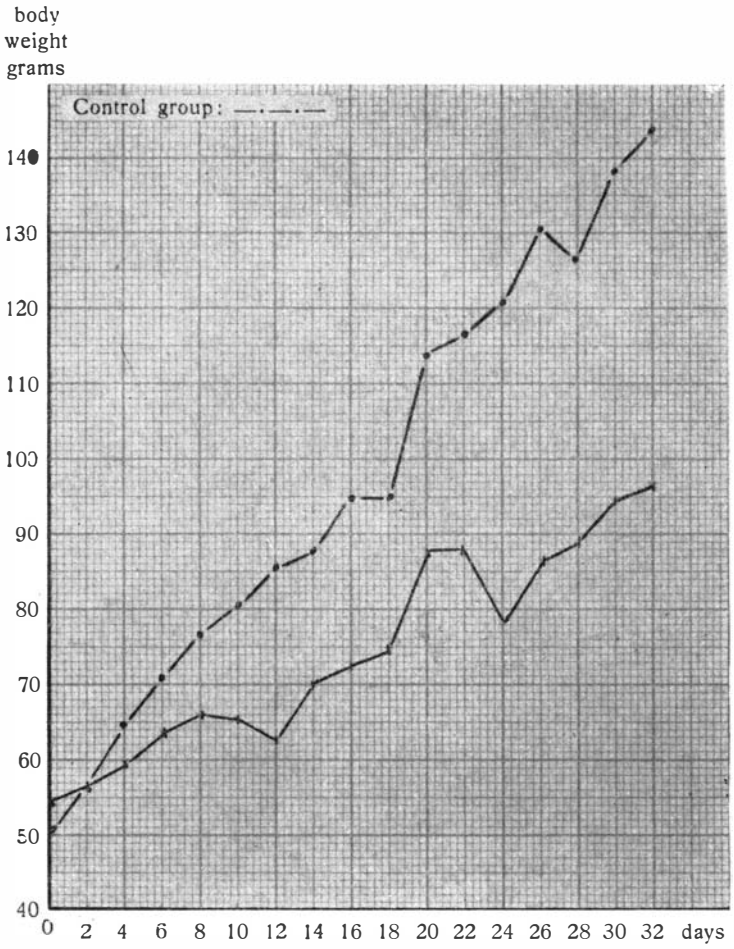

Fig. 4. Average weight curve for the group receiving polar bear liver oil. Experiment 3.

postmortem examination no pathological findings were made which could explain the death apart from subcutaneous hemorrhages, and a possible pericardial bleeding.

The remaining rats were killed and in one case no significant pathological findings were made by postmortem examination. Hemorrhages were found in the remaining three cases. In one case marked hyperemia was found, in another case enlargement of the thyroid, parathyroid and suprarenal gland, and in the third case a large fibroma of the thymus.

In urine collected from this group, Heller's test was strongly positive in two samples, and by microscopical examination in the latter, red blood cells were found.

In one rat which suffered from hemorrhage the hemoglobin was 77 %, and the sedimentation reaction was 1—2 mm.

The first manifestation of clinical symptoms in relation to the time from the beginning of the experiment and the vitamin A dose in the individual rats in this group is given in Table 5.

The average weight curve for this group compared with the control group is given on page 57. During the first ten days of the experiment the average daily weight increase was approximately one third of the normal, and during the first thirty days approximately one half of the normal.

The vitamin A reserve was determined in the liver of two of the rats by the technique described on page 32. The average weight of the liver was 7.5 g. The average yield of oil was 7.5 %, and the average vitamin A content was 309,000 I. U. vitamin A per gram oil, corresponding to 23,100 I. U. per gram liver or 172,900 I. U. in the whole organ.

The average calcium content of the ashed femur was 38.4 % as against 37.5 % in the control group.

From these experiments (Experiment 1, 2 and 3) it may be concluded that the effect of bear liver oil, — the fraction of the bear liver containing the vitamin A, — is identical to the effect produced by bear liver on rats.

c) The Effect of Fat-Free Polar Bear Liver on Rats.

The purpose of this experiment was to study the effect on rats of polar bear liver, where the vitamin A and the fat had been removed, in an attempt to isolate the fraction of the liver that causes the toxic symptoms.

The oil was extracted from the liver in Soxhlet's apparatus by acetone. The extraction was carried out in twenty-four hours and the fat-freed liver was then carefully heated to remove all the acetone. The dried powder was then ground in a mortar and given to the rats in amounts corresponding to 1 gram of the original liver, i. e. 0.5 grams of this powder per rat per day, which was mixed with the ordinary basal diet.

It was so arranged that this food mixture was given in the smallest possible amount to the rat to start with, and later on in the day they were given the amount of ordinary diet they wanted. There was, however, no difficulty in getting the rat to eat this diet mixture.

The condition of the experiment was otherwise exactly the same as for the control group. The rats received the same sufficient diet as given to the control group.

The rats were kept on this diet for one to three months. They were then killed and examined in the same way as the other groups.

Rat No. 3 was given this diet during the first forty-eight days after which it was removed, and the rat was given normal diet from then on. It was found that this made no difference to the condition of the rat.

It was found that the rats in this group were perfectly normal throughout the whole experiment and showed no signs of any ill effect

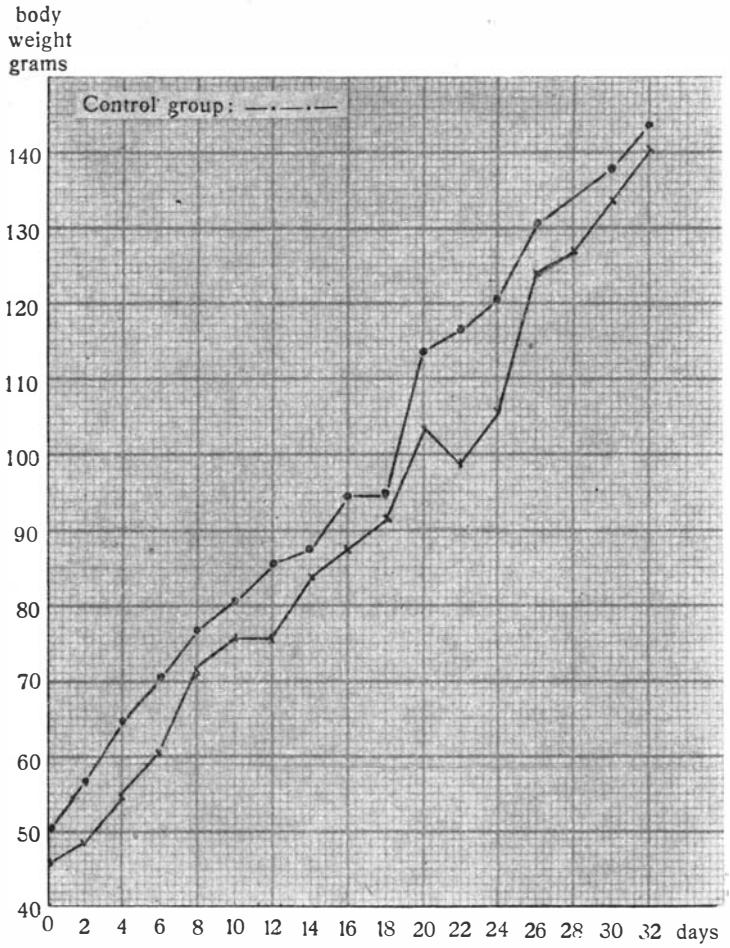

Fig. 5. Average weight curve for group receiving polar bear liver where the vitamin A had been removed.

from the fat-free fraction of the polar bear liver. Their weight curve was perfectly normal compared with the control group. X-ray examination of the bones showed normal conditions, even two months after the beginning of the experiment, and the examination of the blood showed also normal conditions. Examination of the urine showed negative findings as it did in the control group, and the benzidine test in the feces was negative.

The weight increase in this group compared with the control group is shown in fig. 5.

The average initial weight was 45.2 grams. During the first ten days the average daily increase of weight was 3.0 grams, and the entire weight increase at the end of this period was 67.2 % of the initial weight, whereas in the control group the figures were 3.0 g and 59.7 % respec-

tively. During the first thirty days of the experiment the average daily weight increase in this group was 2.9 grams which again is exactly the same as the control. The increase in weight was 194.4 % of the initial weight as against 175.0 % for the control group.

The average daily dose of vitamin A was 20 I. U. per rat corresponding to 0.33 I. U. per gram body weight during the first ten days, and 0.22 I. U. per gram body weight during the first thirty days of the experiment, as against 0.30 and 0.20 for the control group.

The vitamin A reserve was determined in the liver of two of the rats by the technique as described on page 32. The average weight of the liver was 13 g. The average yield of oil was 1.3 %, and the vitamin A content was 26,000 I. U. per gram oil, corresponding to 340 I. U. per gram liver or 4,390 I. U. for the whole liver.

By postmortem examination, no pathological findings were made. Examination of the blood showed normal conditions. (Hemoglobin 110 %, and sedimentation reaction 5—10 mm after one hour.)

By microscopical examination of the liver, kidneys, intestines, spleen, adrenals, testis, thyroid gland, heart, lungs, bones and teeth, no pathological findings were detected. There was, however, slight hyperemia which was probably due to the ether anesthesia.

The average calcium content of the ashed femur was 38.0 % as against 37.5 % for the control group.

From this experiment it may be concluded that bear liver free of vitamin A had no ill effects on rats.

d) The Effect of Vitamin A-Free Polar Bear Liver Oil On Rats.

From the previous experiments, it is evident that the toxic effect of bear liver oil, the fraction of the bear liver containing all the vitamin A, is identical with the toxic effect of bear liver, and that bear liver where the vitamin A had been removed is non-toxic.

In order to ascertain whether the toxic effect of bear liver oil is due to the vitamin A or to the lipids, two rats of approximately the same initial body weight as the other rats in these experiments were given crude bear liver oil, where the vitamin A had been destroyed by long-lasting exposure to sunlight, in amounts corresponding to the doses of the bear liver oil containing the vitamin given to the previously mentioned groups. This dose was given daily for a period of twenty-seven days, at the end of which the rats were killed and examined. The conditions of the experiment were otherwise identical to those for the other groups, and the rats received a sufficient basal diet with vitamins A and D in optimal growth doses.

The oil was partly extracted by alcohol and ether from bear liver (No. 52) and partly by acetone in Soxhlet's apparatus. It was left

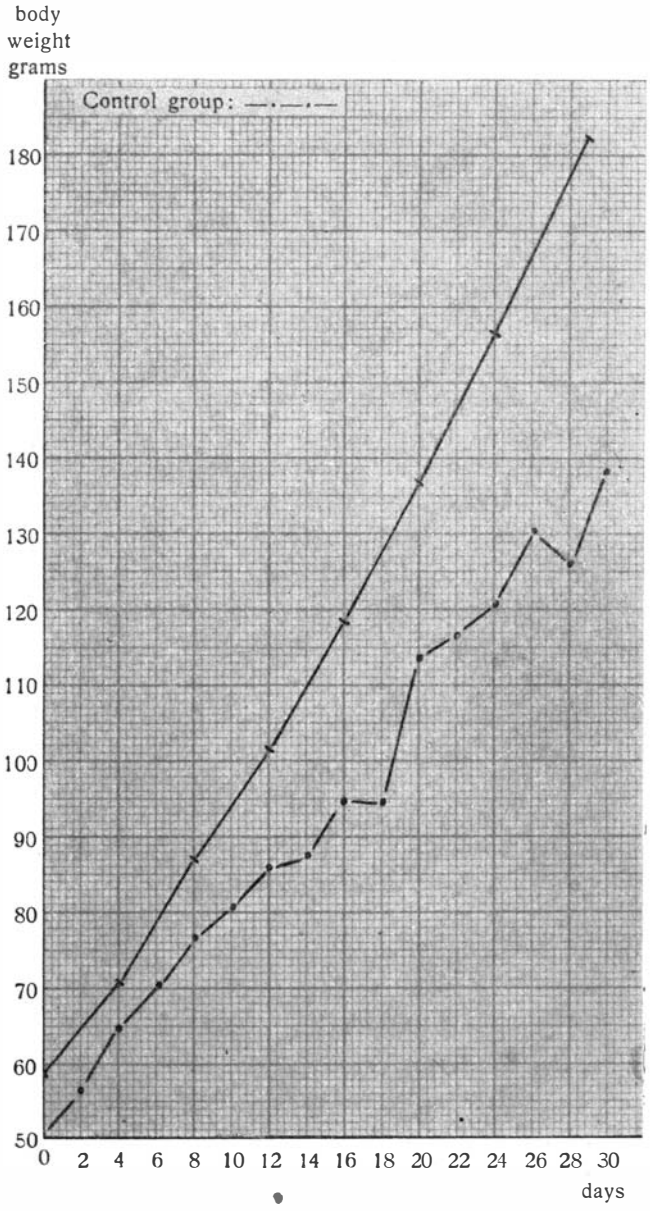

Fig. 6. Average weight curve for group receiving polar bear liver oil free of vitamin A, compared with the control group.

standing exposed to sunlight for ten to fourteen days and finally left boiling on water bath for several hours after adding a few drops of H_2O_2. By the antimony trichloride reaction, all the vitamin A was then found to have been destroyed.

Throughout the experiment the rats appeared perfectly normal, and free of any symptoms. The appetite was good and the weight gain was

4.0 g per day , as against approximately 3.0 g for the control group. Thus the weight gain was considerably higher than in the control rats, which might possibly be explained by the considerable additional fat ingestion in the form of bear liver oil (approximately 0.25 g daily).

By postmortem examination, no pathological findings were made. Apart from slight hyperemia, no pathological findings were made in the kidneys, liver, adrenals, pancreas, testis or bones by microscopical examination of the two rats examined. By sudan staining practically no sudanophilic droplets were found in the adrenal and none whatever in the liver.

The benzidine reaction in the feces gave negative results.

The hemoglobin was 107 % and 102 % respectively. Differential blood count showed normal conditions as compared with the control group, (eosinophils: 1—2 %, "band"forms: 7—8 %, Polymorph.: 8 %, lymphocytes: 87.5—89 %, and monocytes: 1—2.5 %).

The ash content of the femurs was 52.7 % (52.1—53.1) calculated on a dry basis, as against 50.1 % for the control group. The calcium content of the ashed bones was 30.5 % and the phosphorous content was 17.6 %.

From this experiment it may be concluded that bear liver oil free of vitamin A had no ill effect on rats.

e) Comparison Between the Effect of Polar Bear Liver Oil and Purified Vitamin A Concentrate.

The purpose with this experiment was to compare the effect of purified highly concentrated sources of vitamin A in the form of whale liver oil concentrate with bear liver oil, when the two oils were given in approximately the same doses with regard to the vitamin A.

Animals of approximately the same weight were used as in the other groups. The rats received the same sufficient diet, and the conditions for the experiment were otherwise exactly the same.

The doses of vitamin A given to this group varied to some extent. At the beginning of the experiment the daily dose was 18,000 I. U. The average daily dose of vitamin A during the first ten days was 20,800 I. U. vitamin A, corresponding to an average of 357 I. U. vitamin A per gram body weight.

The initial average weight was 47.6 grams. The average increase of the weight during the first ten days of the experiment was 50.6 % of the initial weight, that is 2.4 grams daily, against 59.7 or 3.0 grams in the control group.

During the first thirty days of the experiment the average daily dose of vitamin A was 31,600 I. U., corresponding to an average of 476 I. U.

per gram body weight. During this period the average daily weight increase was 0.97 grams.

At the end of thirty days the weight increase was 61.1 % of the initial weight, as against 175 % for the control group.

S y m p t o m s.

After the first week, the dose was increased to between approximately 25,000 and 35,000 I. U. vitamin A, and the symptoms became more pronounced.

Shortly after the commencement of the experiment, the rats in this group showed signs of drowsiness. Already the second day changes in appearance could be seen, and the rats showed no activity, and looked unwell.

On the tenth day very slight eye symptoms were observed. The following day rat No. 3 showed signs of limping. The fourteenth day of the experiment, the characteristic eye changes: exophtalmus, loss of hair around the eye, swelling of the palpebrae (oedema), and soreness around the eyes were observed in all rats in this group. The following day rats Nos. 1, 2 and 3 showed limping. On the eighteenth day of the experiment, epilation was observed in all rats as well as soreness around the mouth, and two days later all rats in this group were limping. Fractures were observed in three of the rats on the twenty-second day. At the end of thirty days, fractures were detected by X-ray in four out of the five rats and at the end of forty-four days, fractures were found by X-ray in all the rats in this group.

Urine collected between the twenty-sixth and the twenty-seventh day showed few red blood cells per field of vision by microscopical examination, and the benzidine test was positive after 20 seconds. In urine collected again two days later, the benzidine test was positive, and many red blood cells were found (microscopical hematuria). The urine was again examined on the following day, and it was then found that Heller's test as well as the acetic acid test were distinctly positive, whereas the benzidine test was doubtful. Urine examined again on the thirty-second day showed Heller's test and the acetic acid test positive.

The symptoms in the individual rats were as follows:

R a t N o. 1. ♂. After the initial symptoms already described this rat had typical changes in the eyes and also to some extent loss of hair on the eighth day of the experiment. These symptoms seemed to disappear in the course of a few days. A distinct swelling of the palpebrae (oedema) was observed on the fourteenth day, and on the following day the rat limped on the right hind leg. On the eighteenth day of the experiment, loss of hair around the mouth was observed (epilation) and the swelling

around the eyes (oedema) persisted. At this time 539,700 I. U. vitamin A had been consumed, corresponding to an average of 28,400 I. U. vitamin A per day or 591 I. U. per gram body weight.

X-ray examination on the twentieth day of the experiment, revealed distinct fracture in the middle of the humerus of the left fore leg, without us being able to detect it clinically. At the same time the rat showed signs of nervousness. By X-ray examination it was observed that the bones were abnormally thin, and had an abnormal shape (see ill. 38).

The oedema of the palpebrae was inconstant, it came and went. Thus on the twenty-fourth day, distinct oedema of the palpebrae was again observed. That day the rat also limped on both hind legs, where distinct fractures of the tibiae approximately 8 mm below the knee joint were detected by X-ray the following day. X-rays were again taken at the end of one month, at which time considerable callus formation was found in all fractures.

On the thirty-second day of the experiment the rat was killed and examined.

At autopsy some degree of exophthalmus and epilation of the palpebrae as well as around the mouth was observed. There was a large hematoma on the medial side around the fracture of the right hind leg. Otherwise no subcutaneous bleeding was observed and no significant pathological findings were made at autopsy.

By microscopical examination the following findings were made:

Liver: Marked hyperemia.

Kidney: Marked hyperemia throughout the organ, and slight degeneration as well as some necrosis of the tubules, while the glomeruli appeared normal.

Adrenals: Hyperemia. By sudan staining a strongly sudanophilic stained ring in the cortex, while the medulla appeared normal.

Heart: Hyperemia.

Lungs: Some places hyperemia in the thickened alveolar walls.

Testis: Possibly some degenerative changes of the testis epithelium.

Spleen: No significant pathological findings.

Intestinal tract: No significant pathological findings.

Bones: Fractured bone trabeculae, and irregular arrangement of bone structure.

Teeth: Hyperemia in the pulp. Signs of inflammation in the gingiva with infiltration of lymphocytes in patches.

Rat No. 2. ♂. After the initial symptoms, the pelt appeared thin and the characteristic eye changes were observed on the tenth day of the experiment. These eye symptoms disappeared again the following day.

The marked oedema of the palpebrae was again observed on the fourteenth day, and limping was observed the following day. On the

eighteenth day increased limping was observed and also loss of hair around the mouth, at which time oedema of the palpebrae was again observed.

On the twentieth day of the experiment fracture was observed on the left hind leg. By X-ray definite fractures of the left tibia and fibula just below the knee joint were found, and a compound fracture of the left fore leg. Similar changes in the structure of the bones as described for rat No. 1 were observed. There was oedema of the palpebrae and soreness around the eyes.

On the twentieth day of the experiment the total vitamin A consumption was 565,700 I. U. corresponding to an average of 28,200 I. U. per day or approximately 510 I. U. per gram body weight.

On the twenty-fifth day the rat was again X-rayed with the same result.

On the thirty-second day of the experiment the vitamin A was removed from the diet and the rat was left for a further forty-four days on the normal basal diet. It was then seen that when the vitamin A was removed the weight curve started to rise, previously it had been quite level. The interesting observation was that the eye symptoms still occurred inconsistently. Thus eighteen days after the vitamin A had been removed from the diet oedema of the palpebrae was noticed, particularly the left. The oedema was again observed four days later, and on the fifty-sixth day of the experiment loss of hair was seen over the left eye. Two days later, the oedema of the left palpebrae was again present as well as a swelling over the forehead which was understood to be a hematoma.

X-ray examination again took place on the forty-fourth day of the experiment, and it was found that the fracture of the left hind leg was healing.

The rat was killed and examined at the end of seventy-six days from the beginning of the experiment, or forty-four days after the vitamin A had been removed from the diet.

The hemoglobin was 73 %, and the sedimentation reaction 1—2 mm. The blood coagulated within ten minutes.

By postmortem examination large filled coronary arteries were found on the ventral as well as the dorsal side of the heart. Several blood extravasations were found in the pericardium. The suprarenal gland appeared atrophic and small.

By microscopical examination of the kidney, liver, adrenals and teeth the following positive findings were made:

Kidneys: Marked hyperemia and some red blood cells outside the capillaries and slight degeneration of the tubules in some places.

Teeth: Marked hyperemia, and red blood cells outside the capillaries in the pulp, and irregular arrangement of the odontoblasts.

Rat No. 3. ♂. Following the initial symptoms, eye symptoms occurred on the eighth day and the pelt appeared thin. These symptoms were less marked the following day, but a slight oedema of the palpebrae occurred again on the tenth day of the experiment. On the following day, limping of the left hind leg was observed.

Oedema of the palpebrae was again observed on the fourteenth day, and two days later exophtalmus and oedema of the palpebrae were again seen. The rat also appeared drowsy. On the eighteenth day of the experiment, loss of hair around the mouth was observed, and the eye symptoms and limping persisted, although X-ray examination two days later did not reveal any fractures. On the twenty-fourth day of the experiment the oedema of the palpebrae again appeared and the rat limped on the left fore leg as well as the right hind leg. At the end of the first month of the experiment X-ray examination revealed a fracture of the right hind leg. On the thirty-fourth day of the experiment, the rat was killed and examined.

By postmortem examination, it was found that the rat was in relatively good condition. No distinct subcutaneous bleeding was found. The thyroid and parathyroid glands appeared larger than normal. The liver was dark in patches and appeared enlarged. The suprarenal gland also appeared enlarged.

By microscopical examination the following findings are made:

Liver: Hyperemia with scattered red blood cells in the liver tissue, where a large number of vacuoles were seen.

Kidney: Marked hyperemia.

Adrenals: Marked hyperemia.

Heart: Hyperemia.

Lungs: Marked hyperemia and thickened alveolar walls.

Spleen: No pathological findings.

Intestinal tract: No pathological findings.

Testis: No pathological findings.

Bone: Similar changes as described for rat No. 1.

Rat No. 4. ♀. After the initial symptoms previously described, similar changes in the eyes and pelt as described for the other rats in this group occurred on the eighth day of the experiment. Oedema of the palpebrae occurred the fourteenth day, and again on the eighteenth day, at which time loss of hair around the mouth was also observed and limping of the right hind leg. X-ray examination two days later showed negative result. There was a distinct limping, however, and marked oedema of the palpebrae, which persisted several days. Marked loss of hair was found the twenty-sixth day, and the following day certain fracture of the left hind leg was clinically diagnosed.

At the end of the first half of the experiment — the thirty-second day, the vitamin A was removed and from then on the weight increased

rapidly. Nevertheless, alopecia on the back was noted six days after the vitamin A was removed. This loss of hair continued for several days.

On the forty-second day of the experiment, ten days after the vitamin A was removed, limping of the right hind leg, suggesting a fracture, was observed. Two days later a fracture of the right hind leg was revealed by X-ray examination whereas the fracture of the left hind leg had practically healed. On the same day soreness around both eyes could be seen. The fracture was found at the characteristic place at the proximal end of the tibia, and the structure of the bone was as observed in the other rats in this group.

The rat was killed and examined on the forty-seventh day of the experiment. The sedimentation reaction was 1 mm, and the hemoglobin was 83 %. No significant pathologico-anatomical findings were revealed.

By microscopical examination the following findings were made:

Liver: Marked hyperemia.

Kidney: Hyperemia, particularly in the subcortical zone, and possibly slight degeneration of the tubules.

Adrenals: Marked hyperemia.

Spleen: No significant pathological findings.

Pancreas: No significant pathological findings.

Salivatory gland: No significant pathological findings.

Heart: Hyperemia.

Lungs: Marked hyperemia, and thickening of the alveolar walls. Some areas are packed with red blood cells.

Teeth: Marked hyperemia, and hemorrhages in the pulp.

Rat No. 5. ♀. After the initial symptoms as previously described for the other rats in this group, eye symptoms occurred eight days after the beginning of the experiment. On the eleventh day the rat limped on the hind legs. The eye symptoms persisted in varying degrees and on the sixteenth day the rat appeared weak with marked oedema of the palpebrae as well as exophtalmus. Two days later loss of hair was seen around the mouth, and the rat limped on the hind legs, although X-ray examination twenty days after the beginning of the experiment still revealed no fracture.

Twenty-two days after the beginning of the experiment, fracture of the left fore leg was clinically diagnosed, and possible fractures of both hind legs. X-ray examination a week later revealed fracture of both hind legs, situated at the proximal end of the tibia and fibula similar to the other rats in this group.

Twenty-three days after the beginning of the experiment, marked loss of hair over a large area of the abdomen was observed (see ill. 8). This improved towards the end of the experiment, and it could be seen that new hair had grown.

The rat was killed and examined at the end of thirty-four days.

The rat was found to be in a poor condition. By postmortem examinatioin large hematomas were found around the fractures. Otherwise no significant pathological findings were made apart from rather large adrenals.

By microscopical examination the following findings were made:

Liver: Hyperemia and a large number of vacuoles in the liver cells.

Kidney: Hyperemia, and possibly slight degeneration of the tubules. Free blood cells were seen in the lumen of some of the tubules.

Adrenals: Hyperemia.

Spleen: Hyperemia.

Pancreas: Hyperemia.

Intestinal tract: Hyperemia.

Heart: Hyperemia.

Lungs: Hyperemia and thickening of the alveolar walls.

Bones: Similar changes as described for rat No. 1.

Summary of Results.

On the second day of the experiment with purified vitamin A concentrates all rats in this group showed symptoms of general malady similar to the other groups receiving bear liver oil.

Some time later eye symptoms, limping, alopecia and fractures occurred in all rats.

Examination of the urine gave varied results, but in most cases the Heller's test and the acetic acid test were positive, and by microscopical examination of the centrifuged urine, red blood cells were found.

In two cases the whale liver oil was removed from the diet after one month, and a rapid rise in the weight curve was observed. The eye symptoms, however, still occurred inconsistently and a marked loss of hair continued which in one of the rats was observed four weeks after the oil had been removed. In one case fractures occurred two weeks after the vitamin A had been removed from the diet.

In one case where hemorrhage was found, the hemoglobin was 73 %, and in another case where no hemorrhage but fracture was present the hemoglobin was 83 %. In both cases the sedimentation reaction was approximately 1 mm.

The first manifestation of clinical symptoms in relation to the time from the beginning of the experiment and the vitamin A dose in the individual rats in this group is given in Table 6.

The average weight curve for this group compared with the control group is given on page 70. During the first ten days of the experiment, the weight gain was only slightly less than in the control group, while during the first thirty days it was only one third of the normal.

By postmortem examination no significant pathological findings were made in four out of the five rats, apart from hematomas around the fractures, and some enlargement of the adrenal glands in two cases, one of which also showed enlargement of the thyroid and parathyroid gland. In one of the rats, where the excess of vitamin A had been removed from the diet for the last forty-four days of the experiment, hyperemia and pericardial bleeding was found. In this case the adrenals appeared small and atrophic.

The vitamin A reserve was determined in the liver of three of the rats by the technique described on page 32. The average weight of the liver was 8.8 g. The average yield of oil was 6.6 %, and the average vitamin A content was 78,200 I. U. per gram oil, corresponding to 5,160 I. U. per gram liver or 45,400 I. U. for the whole organ.

From this experiment, and from the previously described experiment with bear liver oil, it is evident that the toxic effect of excess of purified vitamin A concentrate is identical to that of bear liver oil, when given in corresponding amounts with regard to the vitamin A content.

Table 6.

The First Manifestation of Clinical Symptoms in Relation to Time from the Beginning of the Experiment and Vitamin A Dose in Rats Receiving Purified Vitamin A Concentrate.

Symptom	No. of days from beginning of experiment until first manifestation of clinical symptoms					Total consumption of vitamin A (I. U.) from beginning of experiment until first manifestation of clinical symptoms				
	Rat No. 1	Rat No. 2	Rat No. 3	Rat No. 4	Rat No. 5	Rat No. 1	Rat No. 2	Rat No. 3	Rat No. 4	Rat No. 5
Poor condition	1	1	1	1	1	18000	18000	18000	18000	18000
Changes in pelts	1	1	1	1	1	18000	18000	18000	18000	18000
Decreased activity	1	1	1	1	1	18000	18000	18000	18000	18000
Drowsiness	1	1	1	1	1	18000	18000	18000	18000	18000
Reduced weight increase.	4	4	4	4	4	72000	72000	72000	72000	72000
Eye symptoms	7	9	7	7	7	126000	172000	126000	126000	126000
Weakness	-	-	-	-	15	-	-	-	-	425000
Limping	14	14	10	17	10	371000	371000	208000	493000	208000
Alopecia	7	17	17	17	17	126000	493000	493000	493000	493000
Soreness around mouth	18	18	18	18	18	516000	516000	516000	516000	516000
Fracture	19	19	30	26	22	539000	539000	950000	770000	608000

f) The Relation Between the Vitamin A Content and Toxicity of Other Arctic Mammalian Livers.

As previously mentioned (see page 15), the livers of certain Arctic mammals other than the polar bear, are also known to be poisonous by the Eskimos, such as the liver of Greenland fox and bearded seal, while livers of snow hare and walrus are considered non-poisonous.

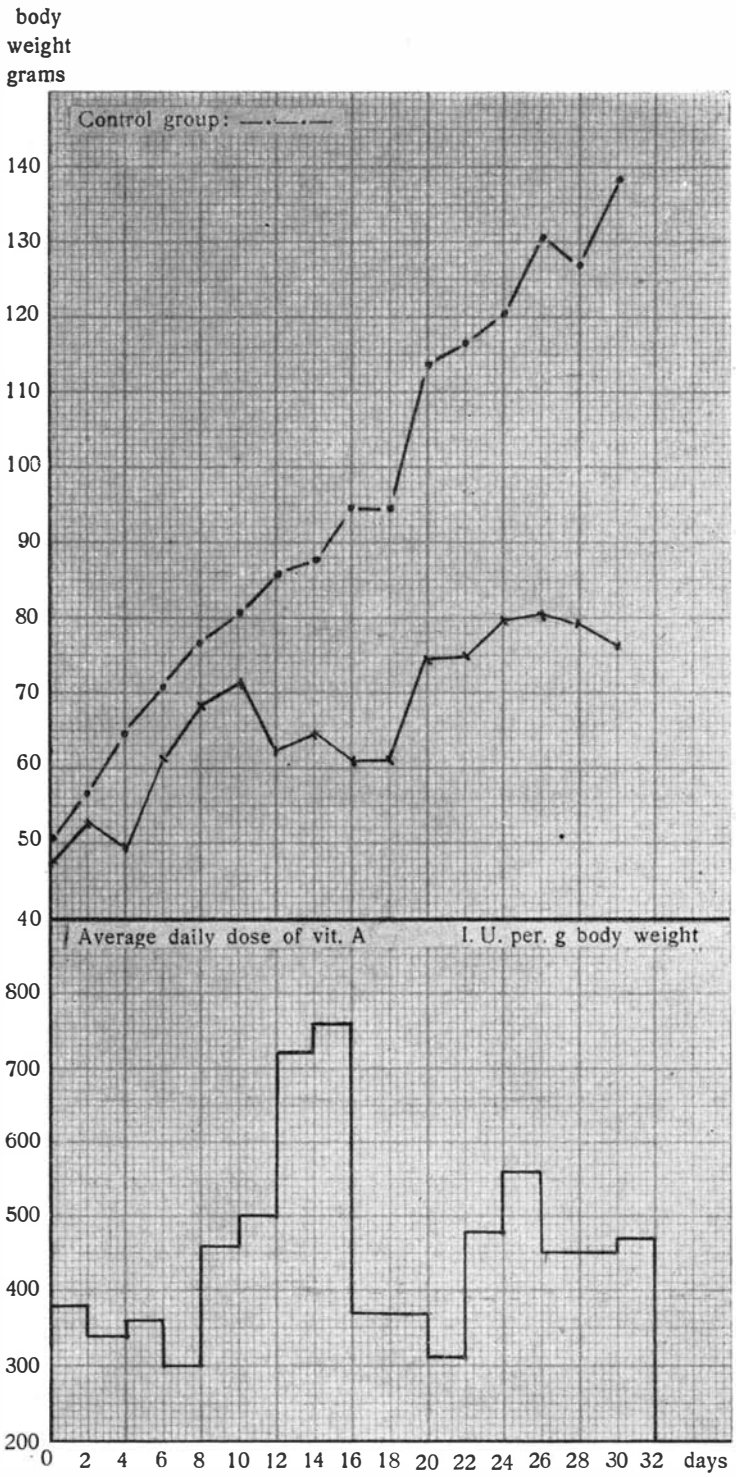

Fig. 7. Average weight curve for group receiving purified vitamin A concentrate (compared with the control group), and the average daily dose of vitamin A.

In connection with the present experiments on the toxic effect of polar bear liver, which was found to be due to excess of vitamin A, it was considered desirable to examine the livers of the above mentioned Arctic mammals with regard to the vitamin A content, in order to see whether there is any relation between the reported toxic effect and vitamin A content of these livers.

During the expedition to Pearyland, North Greenland, livers of Greenland fox, walrus and snow hare were collected. After the return to Norway, the vitamin A content was determined in these livers by the technique described on pages 23—24, with the following results:

1) *Greenland Fox (Canis groenlandicus).*

The liver of a fox (sample No. 40) shot in Pearyland, latitude 82° 30′ N in August 1947, was weighed and preserved in toluene. The sample was kept in a closed tin in a cool place, and on return to Norway was placed in a refrigerator.

After all the toluene had been removed by evaporation, the fat was extracted from the liver as described on pages 23—24. Spectrographical examination of the oil extracted from this liver showed a vitamin A content of 120,000 I. U. of vitamin A per gram fat, corresponding to approximately 12,000 I. U. vitamin A per gram liver. An acurate estimation of the vitamin A content of the liver could not be carried out as part of the fat from the liver had dissolved into the toluene and some of the toluene extract was lost during transport.

From this observation it appears evident, however, that the vitamin A content of liver of Greenland fox is approximately of the same order as that of the liver of bearded seal and polar bear.

2) *Walrus (Odobaenus rosmarus).*

The liver of a young walrus (sample No. 48—1) shot at Cape Herschel, North East Greenland in the summer of 1947, was preserved in brine and examined in the same manner as described for the polar bear.

10 grams were taken from the central part of the liver and extracted by absolute alcohol and ether as described on page 24. The fat obtained was light yellow in colour and by cooling it solidified at room temperature. The yield was 5 %.

By spectrographical examination only traces of vitamin A were found in the fat.

3) *Snow Hare (Lepus variabilis glacialis).*

The liver from a snow hare (sample No. 46) shot in Pearyland in August 1947 was preserved in toluene and examined in the same way as described for the fox liver. The fat was extracted by alcohol and ether and showed by spectrographical examination a vitamin A content of

12,000 I. U. per gram fat, corresponding to approximately 1,200 I. U. vitamin A per gram liver.

It is thus evident that the livers of polar bear (see p. 24), bearded seal (Rodahl & Moore 1943), and Greenland fox, which are known to be poisonous, are very rich in vitamin A, while the livers of walrus and snow hare, which are considered non-poisonous by the Eskimos, contained only small amounts of vitamin A.

These observations therefore support the findings made by experiments on rats with polar bear liver, that the toxic effect of certain Arctic mammalian livers, which are considered by the Eskimos to be poisonous, is due to the very high vitamin A content of these livers, and when ingested in large quantities they may lead to the condition of hypervitaminosis A.

III. Discussion and Summary.

It is of considerable interest to note that the livers of the Arctic mammals which are considered by the Eskimos to be poisonous, such as polar bear, bearded seal, and fox, are found to be very rich in vitamin A.

Thus the average vitamin A content of polar bear is found to be approximately 20,000 I. U., bearded seal 18,000 I. U., and in one sample of Greenland fox approximately 12,000 I. U/g, while the liver of walrus and snow hare, which are eaten by the Eskimos without any sign of ill effect, only have small amounts of vitamin A.

From these observations it may be suggested that hypervitaminosis A may not only follow ingestion of large quantities of polar bear liver, but also livers of bearded seal and Greenland fox.

The liver of one fully grown fox weighed approximately 80 grams, which according to these findings should correspond to approximately 1 million units of vitamin A. It is a question whether this amount is sufficient to produce any symptoms of hypervitaminosis A in man.

There is reason to ask why these Arctic mammals have such an enormous vitamin A reserve in their livers. The vitamin A concentration is naturally an expression of the vitamin A richness in the food. The seal eats a large amount of herring, cod, etc., and the seal liver in its course constitutes again an important part of the food of the polar bear. Thus an increasing accumulation of vitamin A takes place in the livers as one moves up in the animal kingdom, from the fish to the polar bear.

It would perhaps be reasonable to expect that the large accumulation of vitamin A in the bear liver might give rise to hypervitaminosis A in the bear himself, as in our experiments on rats it is found that rats die from hypervitaminosis A long before the vitamin A content per gram liver has reached the level normally found in the polar bear. We know very little about the physiology and the pathology of the bear, however,

which for obvious reasons are not easily investigated, and it is not at all impossible that the large vitamin A reserve in the bear's liver might prove injurious to the bear himself. It is thus possible that some of the pathological findings made by Koettlitz (1898) by the examination of 122 polar bears, such as a high frequency of septic wounds, numerous fractures and various bone abnormalities, may partly be taken as a result of injurious excess of vitamin A. As the majority of the killed bears are caught by trappers for the purpose of collecting the pelts, the bears are not usually examined, and it is possible that a systematical examination of a large number of bears might reveal a high frequency of the mentioned pathological findings, as seems likely from Koettlitz' statements.

It is known that the bear often eats the whole of one seal in a single meal. In the case of bearded seal this would mean that the bear from the seal liver alone probably ingests about 30—100 milion I. U. vitamin A, which corresponds to 60—220 I. U. vitamin A per gram body weight, the average weight of an adult bear being approximately 450 kg. This dose of vitamin A is usually found to give rise to toxic symptoms in rats, when given daily over a period of several days, but it is hardly probable that the bear eats a seal liver every day. Furthermore, it must be borne in mind that the bear, to a large extent, feeds on baby seals or young seals which have a much lower vitamin A reserve in the liver. It is therefore a question whether the single doses of vitamin A consumed by the bear are sufficient to give rise to acute toxic symptoms in the bear, while it is quite possible that the same doses ingested over a long period of time might give rise to symptoms of hypervitaminosis A in the bear.

The three bear livers examined by Rodahl and Moore (1943) were collected in the middle of the winter and contained 18,000; 18,000; and 13,000 I. U. vitamin A/g respectively. The first of these livers was from a two year old female, the second from a four year old male. (In the third case the sex and age of the bear was not known). The two bear livers described in this paper were from five year old female bears collected in the middle of the summer, and showed 21,900 I. U/g and 26,700 I. U/g respectively. It thus appears probable that the vitamin A content of the bear liver might be higher in the summer than in the winter, which might seem likely from our knowledge of the habits of the bear. It is mainly in the spring, summer and autumn that the bear is able to catch a large number of seals along the edge of the pack ice, while in the winter the food is scarce, at which time he, to a large extent, is dependant on the stored body fat. The female bear, moreover, hibernates during a few months in the middle of the winter in snow lairs whilst the cubs are born, during which time no food is consumed. It is also known that the male bear occasionally hibernates in snow lairs in the winter in particularly bad weather.

The individual vitamin A content of the liver appears however to vary considerably, in a similar way to conditions found in other Arctic mammals, such as seals, where in some cases variations from less than 1,000 up to 24,000 I. U. vitamin A per gram liver have been found in the same species of seal (Rodahl, 1949).

The effect of raw bear liver was studied in experimental rats for the first time by Rodahl and Moore (1943), who in some cases produced symptoms identical to hypervitaminosis A, while in other cases no ill effect was observed in rats which consumed nearly as much of the bear liver.

In the present experiments the *toxic effect of bear liver* has been studied more closely.

From these experiments it may be concluded that polar bear liver is poisonous to rats and that the toxic effect increases with the amount consumed, as judged by clinical symptoms.

0.5—0.7 grams of bear liver daily proved lethal in two rats after sixteen to sixty-five days. The surviving three rats had consumed 0.5—0.6 grams of bear liver daily in periods from forty-five to one hundred days without lethal results.

The symptoms caused by bear liver were identical with those observed in rats receiving the oil containing the vitamin A extracted from the same bear liver. Fat-free bear liver without vitamin A had no ill effect on rats, nor had bear liver oil, where the vitaimin A had been destroyed. The bear liver oil had exactly the same effect on rats as purified vitamin A concentrate in the form of whale liver oil when given in corresponding amounts with regard to the vitamin A content. Furthermore, no symptoms other than those following bear liver oil or whale liver oil were observed in any of the rats given bear liver. Finally, the symptoms increased with increasing doses of vitamin A.

It may therefore be concluded that the toxic effect of bear liver depends on its content of vitamin A, or in other words that the toxic factor of bear liver is identical with vitamin A, and that ingestion of large quantities of bear liver by experimental animals leads to the condition of hypervitaminosis A. In this connection it may be mentioned that the liver from a dog, which in another experiment was fed on large amounts of pure vitamin A, had exactly the same effect on rats as bear liver, when given in corresponding amounts with regard to the vitamin A content.

In the same connection it may also be of interest to note that Pavcek, Herbst, and Elvehjem (1945) produced similar symptoms by feeding telangiectatic bovine livers rich in vitamin A to rats in amounts corresponding to approximately 20,000 I. U. vitamin A per rat daily. Equivalent amounts of crystalline vitamin A alcohol, or of vitamin A supplied by halibut liver oil, produced identical toxic symptoms.

The effect of bear liver feeding compared with the effect of excess of vitamin A in the form of bear liver oil or purified vitamin A concentrates, shows that the gross doses of vitamin A producing the various toxic symptoms are approximatively the same, whether the source of vitamin A is bear liver, bear liver oil or purified vitamin A concentrates, as is evident from table 8.

Thus an average daily vitamin A consumption per gram body weight of 325 and 197 I. U. proved lethal in two of the rats receiving bear liver. Similar gross doses of vitamin A proved lethal in three of the rats receiving bear liver oil.

Of the other clinical symptoms of hypervitaminosis A, limping occurred in the rats receiving bear liver on an average about the fourteenth day, after a total consumption of approximately 210,000 I. U. vitamin A. The same symptom usually occurred in the groups receiving bear liver oil or purified vitamin A concentrate from the ninth to the thirteenth day after an average total consumption of approximately 140,000 to 330,000 I. U. vitamin A.

Eye symptoms occurred in the group receiving bear liver after fourteen days, after a total consumption of approximately 235,000 I. U. vitamin A, as against an average of seven to twelve days, and 130,000 to 265,000 I. U. vitamin A for the groups receiving bear liver oil or purified vitamin A concentrates.

Fractures occurred in the group receiving bear liver after an average of about thirty- seven days, after a total consumption of approximately 560,000 I. U. vitamin A. In the groups receiving bear liver oil or purified vitamin A concentrates, the same symptom occurred after an average of eleven to twenty-three days, after a total consumption of approximately 230,000 to 680,000 I. U. vitamin A.

Soreness around the mouth occurred at the end of ten to fifty-five days in rats receiving bear liver, as against an average of nine to eighteen days in the other groups, after a total consumption of approximately 190,000 to 800,000 I. U. vitamin A (as against an average of approximately 140,000 to 516,000 I. U. vitamin A for the other groups).

Alopecia occurred at the end of sixteen and sixty-five days after a total consumption of approximately 300,000 and 960,000 I. U. vitamin A, as against an average of six to fifteen days and approximately 100,000 to 420,000 I. U. vitamin A for the other groups.

After forty-five days the bear liver was removed from the diet in one of the rats, and a marked rise in the weight curve was observed. Nevertheless eye symptoms with blood crusts and small hemorrhages around the eyes and mouth persisted until the rat was killed fifty days after the bear liver was removed from the diet. Similar observations were made in rats which had been receiving excess of purified vitamin A concentrates.

In the urine Heller's test and the acetic acid test were found to be positive, and red blood cells were found in the urine after two months of the experiment in the rats receiving bear liver. In the feces, the benzidine test was positive. The same findings were made in the urine and feces from rats receiving bear liver oil or purified vitamin A concentrates.

The hemoglobin was determined in three of the rats given bear liver and found to be 88; 89; and 81 %, the colour index being 0.8, 1,0 and 0.8 respectively. The blood coagulated within 5 minutes. Differential blood counts revealed no pathological changes. Examination of the blood from the rats receiving bear liver oil or purified vitamin A concentrates revealed similar findings.

By postmortem examination no significant pathological findings were made in three of the rats receiving bear liver. In the other two rats subcutaneous and visceral hemorrhages were found as well as hyperemia. In one case a sharp bending of the spine was observed and in one case the teeth appeared brittle. Apart from the last two observations, similar findings were made in rats receiving bear liver oil or purified vitamin A concentrates.

Reduction in the normal weight increase is one of the earliest and most constant symptoms in the rats receiving bear liver, which is also the case in rats receiving bear liver oil or purified vitamin A concentrates.

There appeared to be no significant changes in the mineral content of the bones in the rats receiving bear liver compared with the control groups. Again similar findings were made in rats receiving bear liver oil or purified vitamin A concentrates.

No other toxic substance apart from vitamin A has been detected in salted bear liver.

As bear liver had only a very slight antirachitic effect, the liver could under no circumstances give rise to hypervitaminosis D. Furthermore the whale liver oil used for control purposes contained no vitamin D whatever. In accordance with this the symptoms produced in this experiment resembled in no way those of hypervitaminosis D. Furthermore, no pathological changes in the calcium metabolism were detected in rats receiving bear liver.

With these findings in view it is possible to explain why some bear livers have proved to be poisonous and others not, when eaten by Arctic travellers. The variability in the vitamin A content is considerable, and it is thus evident that small quantities of a liver containing a relatively small amount of vitamin A may be eaten without ill effect, while the same amount of a liver rich in vitamin A eaten in larger quantities would cause symptoms of hypervitaminosis A.

These findings explain why those who only ate a small amount of bear liver suffered no injury, while those who ate large quantities of

the liver suffered invariably. It is calculated that 250—500 grams of bear liver must have been eaten by some Arctic travellers, reported in the literature (see page 19), with ill effect, which should correspond to between 5 and 10 million I. U. vitamin A consumed by one man in a single meal. Ill effect has previously been reported (see page 22) in man after ingestion of 6 million I. U. in the form of halibut liver oil.

These observations in man support the findings made by experiments on rats, that the toxic factor in the bear liver is identical with vitamin A.

The fact that some observers had found the bear liver to be less toxic when well done (well fried), might possibly be explained by the fact that some of its content of vitamin A is destroyed by thorough frying.

It is generally found that it is the older animals that have the highest vitamin A reserve in the liver, which might explain the fact observed by the Eskimos that livers from older animals are more toxic than those of young animals.

Table 7 shows the gross dose of vitamin A which proved to be lethal to rats in this experiment.

Table 7.

Showing Lethal Doses of Vitamin A.

Condition of Experiment	Rat	Total Dose of Vit. A, I. U.	I. U. Vit. A per Gram Body Weight per Day	I. U. Vit. A per Day	No. of Days
Basal Diet + Bear Liver ...	No. 1	965500	197	14800	65
	No. 4	305800	325	19100	16
Basal Diet + Bear Liver Oil	No. 2	265000	384	22000	13
	No. 4	265000	384	22000	13
	No. 5	265000	428	22000	13
Basal Diet II + Bear Liver Oil	No. 2	183000	274	18300	11
Mean		374000	330	19700	21

From table 7 it is evident that in some cases doses from 274 I. U. to 428 I. U. vitamin A per gram body weight proved lethal within eleven to sixteen days, while in one case 197 I. U. vitamin A per gram body weight proved lethal at the end of sixty-five days.

The experiments described were originally planned to study the symptoms caused by various fractions of bear liver compared with excess of vitamin A from other sources, and not to determine the exact lethal dose. From these experiments it may be suggested however that the lethal gross dose of vitamin A in rats may be in the order of 300 to 600 I. U.

vitamin A per gram body weight, depending on the duration of the experiment, while the toxic dose is considerably less, probably 50 to 100 I. U./g body weight. These figures must be taken as maximum values however, as later experiments have shown that 30 to 40 % of the ingested amount of vitamin A was lost through feces.

By careful daily examination of the individual rats in each group during the experiment, the first manifestation of the *clinical symptoms* was recorded in relation to the time from the beginning of the experiment and the consumption of vitamin A. A summary of these observations is given in table 8.

Table 8.

Showing First Manifestation of Clinical Symptoms in Relation to Time from the Beginning of the Experiment and Vitamin A Dose. Average.

Symptoms	No. of days from beginning of experiment until first manifestation of clinical symptoms				Total consumption of vitamin A (I. U.) from beginning of experiment until first manifestation of clinical symptoms			
	Basal diet + bear liver	Basal diet + bear liver oil	Basal diet II + bear liver oil	Basal diet + purified vit. A concentrate	Basal diet + bear liver	Basal diet + bear liver oil	Basal diet II + bear liver oil	Basal diet + purified vit. A concentrate
Poor condition	-	2	1	1	-	32000	16000	18000
Changes in pelts	-	2	1	1	-	32000	16000	18000
Decreased activity	-	2	1	1	-	32000	16000	18000
Drowsiness	-	2	-	1	-	32000	-	18000
Reduced weight increase	12	4	2	4	240000	73000	32000	72000
Weakness	-	2	1	15	-	32000	16000	425000
Stiffness in limbs	-	7	5	-	-	128000	88000	-
Limping	14	9	9	13	210000	181000	142000	330000
Alopecia	40	9	6	15	635000	163000	109000	420000
Soreness around mouth	37	9	9	18	588000	163000	140000	516000
Eye symptoms	14	12	8	7	235000	265000	130000	135800
Diarrhea	-	-	13—14	-	-	-	292600	-
Fracture	37	11	21	23	564000	228000	545000	681000
Death	40	13	11	-	635000	289000	215000	-

From table 8 and from the previous description of the experimental rats, it appears evident that some of the symptoms occurred in direct connection with the first doses of vitamin A as some sort of acute intoxication, while other symptoms occurred when the excess of vitamin A had been given to the animals for some time. The symptoms occurred constantly in all groups, and there was a reasonable agreement with the first manifestation of the symptoms in relation to the time from the beginning of the experiment and the dose of vitamin A from one group to another.

The symptoms may be divided into symptoms of acute intoxication and symptoms of more chronic intoxication.

Of these, the acute intoxication symptoms appear to be signs of general malady and unwell-being, with changes in the pelts, drowsiness, weakness, and decreased activity. These symptoms may well be compared with those observed in man and dogs following ingestion of bear and seal liver.

The symptoms following chronic intoxication appear to be: Reduced weight gain, limping, stiffness in the limbs, alopecia, soreness and bleeding in the skin, and eye symptoms such as exophthalmus, loss of hair and soreness around the eyes, as well as swelling of the palpebrae (oedema), and finally fractures. All these symptoms appear to be of a more serious nature, and indicate pronounced pathological changes in the organs. Of these symptoms only alopecia has been reported to occur in man and dogs, after eating large quantities of bear liver and other livers of Arctic mammals rich in vitamin A. It must be noted, however, that in this experiment the bear liver and other sources of vitamin A were given daily over a long period, while bear and seal livers were eaten at a single meal by the Arctic travellers.

In the group receiving bear liver, the symptoms of acute intoxication at the beginning of the experiment did not occur, and some of the other symptoms, such as alopecia and soreness around the mouth occurred later than in the other groups. This may be explained by the fact that the consumed amount of vitamin A was less than in the other groups, due to the reluctance of the rats to eat the bear liver. This was particularly noticeable at the beginning of the experiment when only very small amounts of liver were consumed before one succeeded in making the liver more palatable to the rats.

Of the symptoms following chronic intoxication, the stiffness in the limbs occurred first, followed by eye symptoms, limping, alopecia and finally fracture.

Alopecia was observed in two of the rats receiving boiled bear liver mixed in the diet, while none of the rats receiving the same amount of bear liver mixture, where the vitamin A had been removed, suffered from alopecia. In all rats receiving bear liver oil or whale liver oil by dripping pipet alopecia occurred, while none of the rats receiving the same amounts of bear liver oil, where the vitamin A had been destroyed, suffered from alopecia.

Alopecia may therefore, at least to some extent, be taken as a specific symptom of hypervitaminosis A.

On the other hand it was observed in some cases that the hair around the mouth became smeared with oil during feeding. The rats tried to remove the oil by their fore legs and by this the hair was possibly rubbed off. Furthermore it has been noticed, in some cases, that the rats rubbed their mouths and noses against the cage in order to remove the oil with the result that the hairs were rubbed off. It has also been observed that the loss of hair was more marked when the oil was thick

and sticky. These observations seem to suggest that also mechanical factors, to some extent, might be at play with regard to the loss of hair observed in rats receiving excess of vitamin A orally.

Stiffness and pains in the legs did not always prove to be due to fracture or hemorrhage, as in some cases distinct symptoms indicating pains in the legs (stiffness, limping, crying by touching or manipulation) were present without fractures being detected by X-ray examination, or bleeding being observed by postmortem examination.

It is therefore a question whether possible pathological conditions in the bones themselves might be the cause of pains. In most cases, however, the limping was found to be caused either by fracture or hemorrhage, or by both.

In the rats which were given bear liver mixed in the diet, soreness around the mouth and eyes occurred in rats Nos. 2, 3, and 4. It appears therefore that these symptoms cannot entirely depend on the mechanical and local effect of the oil, but that they, in some cases at least to some extent, may depend on a specific action of excess of vitamin A. Furthermore, the same large doses of oil given to the rats by pipet or mixed in the diet did not cause any soreness when the vitamin A was destroyed. Finally fat-free bear liver mixed in the diet in amounts corresponding to the amounts of bear liver given to the mentioned group, did not cause these symptoms.

In this connection it may be of considerable interest to note that the above mentioned symptoms in some cases persisted in hypervitaminotic rats for a considerable time after the excess of vitamin A was removed from the diet. Thus in one rat, which during a period of forty-five days had been fed on bear liver mixed in the basal diet, eye symptoms with blood crusts and small hemorrhages around the eyes and mouth persisted until the rat was killed fifty days after the bear liver had been removed from the diet. This clearly illustrates that the mentioned symptoms may exist in hypervitaminotic rats without being caused by any mechanical or local effect of the oil or the liver. In this case it may be probable that during the first forty-five days of the experiment enough vitamin A had been stored in the organs to maintain some of the symptoms of hypervitaminosis A.

Similarly, it was found in one of the rats in the group receiving whale liver oil, that when the whale liver oil was removed from the diet after one month, a rapid rise in the weight curve was observed, while eye symptoms still occurred at intervals. Marked loss of hair was observed in one of the rats four weeks after the oil had been removed. Furthermore, fractures occurred long after the vitamin A had been removed from the diet.

It thus seems evident that the established reserves of vitamin A in the organs of hypervitaminotic rats are sufficient to maintain the

symptoms, or that the already established pathological changes in the organs are of more permanent nature, persisting some considerable time after the vitamin A is removed from the diet. It seems probable that both these possibilities are the case.

Absence of the normal *weight gain* in young growing rats was found to be one of the first symptoms in this experiment following ingestion of large doses of vitamin A in the form of bear liver, bear liver oil or whale liver oil. This reduction of the weight increase was probably due to reduced food consumption as a result of loss of appetite in the experimental animals.

The relation between the vitamin A consumption and the weight increase is given in tables 9 and 10.

From table 9 it is evident that the weight increase is less than the normal in all groups receiving excess of vitamin A, but during the first ten days of the experiment, however, there is no obvious relation between the vitamin A dose and the weight increase. It must be noted, however, that one had no exact record of the absorbed amount of vitamin A, as the gross dose could not directly be taken as a measure for this.

From table 10 it is evident that there is a marked reduction in the weight increase in rats given excess of vitamin A, and during the first thirty days of the experiment there is a clear relation between the vitamin A dose and the weight increase when the vitamin A was given in great excess, the higher the dose, the greater is the reduction in the weight increase. 362 I.U/g body weight thus reduced the weight increase to approximately half of the normal, 476 I. U/g to approximately one third of the normal.

It appeared as if the reduction in the weight increase was caused by lack of appetite, resulting in a decrease in the food intake, as a rapid improvement of the appetite and rise of weight curve followed separation of the excess of vitamin A.

By examination of the *blood* a slight hypochromic anemia was found in some of the hypervitaminotic rats, but in most of these cases hemorrhages were found, which could explain the anemia (bleeding anemia).

In practically all cases the blood coagulated normally. The sedimentation reaction was found to be less in the hypervitaminotic rats than in the control group. The prothrombin time was examined in one of the hypervitaminotic rats, and found to be normal (16″), as was the fasting blood sugar (83 mg/100 ml as against 88 mg/100 ml in a normal rat).

No significant change in the differential blood count was observed in the hypervitaminotic rats as compared with the control group, as is evident from tables 12 and 13. There appeared to be a decreased resistance against infection in the hypervitaminotic rats, and some of the

Table 9.

Showing the Average Vitamin A Consumption and the Weight Increase During the First Ten Days of the Experiment.

Condition of the Experiment	Average Initial Body Weight. Grams	Average Weight Throughout the First Ten Days. Grams	Average Increase of Weight in % of the Initial Body Weight at the End of 10 Days	Average Daily Increase of Weight During 10 Days. Grams	Average Daily Dose of Vit. A. (I. U.) During the First 10 Days	Average Dose of Vit. A. per g Body Weight During the First 10 Days (I. U.)
Basal Diet (Control)...	50.2	66.3	60 %	3.0	20	0 3
Basal Diet + Bear Liver	44.8	55.0	53 %	2.3	15160	275
Basal Diet + Bear Liver Oil	50.9	57.6	30 %	1.5	19630	340
Basal Diet II + Bear Liver Oil	54.7	61.0	20 %	1.1	18320	300
Basal Diet + Purified Vit. A. Concentrate..	47.6	58.3	51 %	2.4	20830	357
Basal Diet + Bear Liver Free of Vitamin A ..	45.2	59 3	67 %	3.0	20	0.3

Table 10.

Showing the Average Vitamin A Consumption and the Weight Increase During the First Thirty Days of the Experiment.

Condition of the Experiment	Average Initial Body Weight. Grams	Average Weight Throughout the First 30 Days. Grams	Average Increase of Weight in % of the Initial Body Weight at the End of 30 Days	Average Daily Increase of Weight During the First 30 Days. Grams	Average Daily Dose of Vit. A. During First 30 Days (I. U.)	Average Dose of Vit. A. per g. Body Weight During the First 30 Days (I. U.)
Basal Diet (Control)...	50.2	97.0	175 %	2.9	20	0.2
Basal Diet + Bear Liver	44.8	73.8	164 %	2.4	16780	227
Basal Diet + Bear Liver Oil	50.9	-	-	-	-	-
Basal Diet II + Bear Liver Oil	54.7	73.1	95 %	1.7	26470	362
Basal Diet[1] + Purified Vit. A. Concentrate .	47.6	66.5	61 %	1.0	31699	476
Basal Diet + Bear Liver Free of Vitamin A ..	45.2	89.7	194 %	2.9	20	0.2

[1] In this case the rats were at one period frequently kept fasting for the purpose of collecting urine samples, and it is possible that this to some extent might have effected the weight curve.

Table 11.

Showing the Results of Blood Examinations.

Condition of the Experiment	Rat No.	Hb %	Red Blood Cells, Millions per 1/1000 ml	Colour Index	Coagulation Time, min.	Sedimentation reaction, mm
Basal Diet (Control)	1	114	-	-	5	10
	3	101	-	-	5	-
	5	95	-	-	5	5
Basal Diet + Bear Liver	2	88	5.16	0.8	5	-
	3	89	4.78	1.0	-	-
	5	81	5.24	0.8	-	-
Basal Diet + Bear Liver Oil (1)	1	100	-	-	5	3
Basal Diet + Bear Liver Oil (2)	1	78	-	-	5	-
	2	86	4.40	0.9	5	-
	3	104	6.22	0.8	5	-
	4	99	5.50	0.9	5	-
Basal Diet II + Bear Liver Oil	1	88	-	-	5	3
	5	77	-	-	10	2
Basal Diet + Purified Vit. A. Concentrate	2	73	-	-	-	2
	4	83	-	-	-	1
Basal Diet + Bear Liver Free of Vit. A	1	110	-	-	5	10
Basal Diet + Bear Liver Oil Free of Vit. A	1	107	-	-	-	-
	2	102	-	-	-	-

Table 12.

Showing the Results of Differential Blood Count. %.

Condition of the Experiment	Rat No.	Eosino-phils	Band forms	Poly-morph.	Lympho-cytes	Mono-cytes
Basal Diet (Control)	1	-	1	12	79	9
	5	-	-	10	90	1
Basal Diet + Bear Liver	2	1	1	15	81	4
Basal Diet + Bear Liver Oil (1)	1	1	-	16	83	1
Basal Diet + Bear Liver Oil (2)	3	1	-	8	90	1
Basal Diet II + Bear Liver Oil	3	1	1	15	82	3
	4	1	1	7	91	1
	5	1	-	5	95	-
Basal Diet + Purified Vit. A. Concentrate	1	2	1	11	86	1
	2	2	-	11	87	-
	3	1	2	6	78	14
	4	1	2	6	85	7
	5	3	1	14	80	3
Basal Diet + Bear Liver Free of Vit. A	1	2	1	10	88	1
	2	1	2	8	84	5
	5	1	1	9	86	3
Basal Diet + Bear Liver Oil Free of Vit. A.	1	2	8	8	88	3
	2	1	1	8	89	1

Table 13.

Showing the Results of Differential Blood Count. %. Average.

Condition of the Experiment	Eosino-phils	Band forms	Poly-morph.	Lympho-cytes	Mono-cytes
Basal Diet (Control)	-	1	11	84	5
Basal Diet + Bear Liver	1	1	15	81	4
Basal Diet + Bear Liver Oil (1)	1	-	16	83	1
Basal Diet + Bear Liver Oil (2)	1	-	8	90	1
Basal Diet II + Bear Liver Oil	1	1	9	89	2
Basal Diet + Purified Vit. A. Concentrate	2	2	10	83	6
Basal Diet + Bear Liver Free of Vit. A	1	1	9	86	3
Basal Diet + Bear Liver Oil Free of Vit. A	2	5	8	88	2

rats that died during the experiment with symptoms of hypervitaminosis A, showed signs of peritonitis and pneumonia.

By *postmortem examination,* no pathological findings were made in the group which received the fat-free bear liver deprived of its vitamin A content, or in the group which received bear liver oil when the vitamin A content had been destroyed.

In many cases macroscopical postmortem examination revealed surprisingly few pathological findings in view of the pronounced clinical symptoms which had manifested themselves in the rats receiving excess of vitamin A in the form of bear liver, bear liver oil or whale liver oil. In some cases no significant pathological changes were observed in the organs by macroscopical examination of these rats. Moreover, in some instances when the rats died from excess of vitamin A with pronounced symptoms of hypervitaminosis A, no pathological findings whatever were revealed by careful postmortem macroscopical examination which could be taken as the cause of death. Prior to death the rats showed marked loss of weight and gradually increasing weakness.

Otherwise the most significant symptoms were hemorrhages associated with hyperemia, and fractures.

The hemorrhages appeared to be quite general, both subcutaneous and visceral. Most of these hemorrhages were scattered and relatively small, and in none of the cases they appeared to be fatal. There appeared to be a general tendency to bleeding, — both in the internal organs, through the kidneys and intestines, as well as through the roughness of the skin around the mouth and eyes, but in no cases did any rat bleed to death.

Bleeding often occurred in places where no serious mechanical injury was likely to start the bleeding, such as in the internal organs like the liver and the pericardium. Moreover, no abnormality was found in the blood coagulation as judged by the rough clinical methods, and the prothrombin time was found to be normal in the one case examined.

In some cases marked arterial hyperemia was found, the cause of this hyperemia could not be decided from the present investigations. In some cases there appeared to be moderate enlargement of some of the internal secretory glands such as the adrenals, thyroid and parathyroid glands, while in one case where the vitamin A had been removed for forty-four days the adrenals appeared to be atrophic and small. In some cases auxiliary adrenals were found.

The second important symptom — the fractures — occured in all of the rats receiving bear liver, all of those that received whale liver oil, and practically all of the young rats that received bear liver oil. This symptom occurred late in the experiment, usually twenty to forty days from the beginning of the experiment after a total consumption of 500,000 —1,000,000 I. U. vitamin A after signs of pathological changes in the bones had manifested themselves for some time, in the form of stiffness in the legs and limping. The fractures occurred in most of the cases at the ends of the long bones, and particularly at the proximal end of the tibia and fibula. The bones were so fragile that by limited movement of the rats in the cage, fractures occurred. It must also be noted that the hypervitaminotic rats were less subject to violence than normal rats, as they showed decreased activity and generally sat quietly in a corner of the cage. In several cases in further experiments, it has been observed that the rats fractured the legs by pressing the leg against a persons hand during dosing.

Complete healing of the fractures was found to take place without any hindrance, and was completed just as quickly as in normal rats where fractures were produced artificially for comparison. In several cases the fractured extremity healed in a wrong position. In some cases new fractures occurred in the same bone which had previously been fractured, although fractures in no case occurred in the same place twice.

It was found that the ash content of the dry bones was approximately the same in the hypervitaminotic rats, as compared with the control group which again was practically identical with that of the groups which received bear liver oil where the vitamin A had been destroyed, or bear liver where the vitamin A had been removed. Furthermore the calcium and phosphorous content of the ashed bones was practically the same in hypervitaminotic rats as in the control group as is evident from table 14.

It thus appears that there is no decrease in the mineral content of the bones of the hypervitaminotic rats as compared with the control rats, at the same time as fragility and a tendency to spontaneous fractures occurred. This fragility, therefore, is hardly caused by decalcification of the bones, as is stated in earlier publications on hypervitaminosis A. Nor was it found that hypervitaminosis A caused any softening of the bones

Table 14.

Showing Average Ash and Mineral Content of the Bones (Femurs).

Condition of the Experiment	Ash in % of the Dry Bone	% Ca in Ash	% P in Ash
Basal Diet (Control)	50.1	37.5	18.3
Basal Diet + Bear Liver	51.8	33.6	18.6
Basal Diet + Bear Liver Oil (1)	-	35.3	-
Basal Diet + Bear Liver Oil (2)	55.9	35.7	18.7
Basal Diet II + Bear Liver Oil	-	38.4	-
Basal Diet + Bear Liver Free of Vit. A	-	38.0	-
Basal Diet + Bear Liver Oil Free of Vit. A	52.7	30.5	17.6

as described by other workers. On the contrary it was found that the bones proved to be abnormally brittle. In this connection it may be of interest to note that also the teeth appeared brittle. Microscopical examination of the bones showed subperiostal hemorrhages, normal density of the bone cells, and irregularity of the bone spicules.

It therefore seems possible that changes in the organic component of the bone might be responsible for the tendency to fractures.

Of the *microscopical findings*, hyperemia, scattered red blood cells outside the capillaries in the internal organs, such as the liver and kidney, slight degeneration of the renal tubules and deposits of sudanophil droplets in and between the liver cells (in the Kupffer cells) appear to be the most constant findings.

The scattered red blood cells which were seen outside the capillaries seemed to indicate an abnormal permeability of the capillary wall for the red blood cells. In the kidneys free blood was seen in the space of Bowman's capsule and in the tubules in several cases thus explaining the hematuria which was frequently observed in the hypervitaminotic rats.

Proteinuria occurred frequently in hypervitaminotic rats. There was also swelling of the palpebrae (oedema), and the secreted amount of urine in twenty-four hours appeared to be less in hypervitaminotic rats, as compared with the control animals.

It would seem natural to consider the described histological changes in the kidneys in relation to the observed proteinuria, and the observed signs of disturbances in the renal function and fluid balance.

In urine from the hypervitaminotic rats, protein and blood were detected after the excess of vitamin A had been given for some considerable time. At the early stages of hypervitaminosis A these symptoms appeared to be inconsistent, but occurred invariably at the later stages. While the hematuria was very intensive, the protein reactions were seldom very strong.

Although the deposits of sudanophil droplets in the liver in some cases were very marked, no clinical signs of hepatic insufficiency were

observed, and the serum colour, determined by Meulengracht's method, was in no case increased. It was remarkable that only few sudanophil droplets were detected in the actual liver cells, while large droplets were deposited between the liver cells (Kupffer cells).

In some cases pneumonia was observed and slight hemorrhages in the intestinal wall. The benzidine test in the feces was positive in the hypervitaminotic rats in the majority of cases, — while it was negative in the control group. No ulcerations were observed in the intestinal tract, however, and it is a question whether the scattered red blood cells outside the capillaries in the intestinal wall would be sufficient to explain the positive benzidine reaction.

By sudan staining of the adrenals, a much larger number of sudanophil droplets were found in the cortex, than in the adrenals of the control rats. Deposits of sudanophil droplets formed in some cases, a continuous broad band, which was stained deep red at the periphery of the cortex, and which also involved a large part of the zona fasciculata. By hematoxylin-eosin staining a large number of vacuoles were observed in the cortex, and the cortex cells in the zona fasciculata appeared irregularly arranged. In all cases the medulla appeared normal.

Systematical *X-ray examination* of the long bones in hypervitaminotic rats at various stages of the experiment showed that the bones gradually became abnormally thin. This reduction in the diameter of the bones particularly involved the bone shaft, while the epiphysis appeared to be more or less of normal width. This was particularly noticeable at the proximal end of the tibia, where the comparatively broad epiphysis looked as if it was swollen compared with the abnormally thin shaft. A series of roentgenograms showed that the broadness of the epiphysis more or less remained normal, or only a moderate decrease was observed, while the thinning of the bone shaft progressed (see illustrations: 22, 23, 29, 33, 34, 35 and 36).

This decrease in the diameter, which occurred early in the hypervitaminotic rat, involved the entire bone, including the cortical shadow, which was often only represented by a narrow white line. In some cases it was observed that the cortical shadow was absent at both ends of the bones, and when the periost was removed at postmortem, only spongy and no compact bones was found at the mentioned places.

Apart from the described reduction in the diameter of the bone shaft, a deformity was simultaneously observed taking the form of a depression in the compact bone usually 8—10 mm from the proximal end of the tibia.

At this particular place fracture usually occurred at a later stage. The line of fracture was either oblique or transverse.

Other typical locations of the fractures were: at the middle of the humerus, and at the distal end of the radius and the ulna. It is probable

Table 15.

Vitamin A Content of Rat Livers. Average.

Condition of the Experiment	% Oil	I. U. Vit. A per g Oil	I. U. Vit. A per g Liver	I. U. Vit. A in Whole Liver
Basal Diet (Control)	2.1	38600	810	8100
Basal Diet + Bear Liver	4.9	175000	8500	21000
Basal Diet + Purified Vit. A concentrate	6.6	78200	5160	45400
Basal Diet II + Bear Liver Oil	7.5	309000	23100	172900
Basal Diet + Bear Liver Free of Vit. A	1.3	26000	340	4390

that the fractures occured at these particular locations because of mechanical factors, as the pathological changes in the bones, as judged by the roentgenograms, appear to be quite general apart from the previously described abnormality at the proximal end of the tibia.

In all cases examined in the present experiments, only one fracture occurred in the tibia, while two fractures often occurred in the fibula. In no case was there fracture in the tibia only, without fracture also being detected in the fibula. In some cases fractures of the proximal tibial metaphyses, just distal of the epiphyses, occurred. In some cases there was disunion of the epiphyses.

Out of the thirty fractures, eighteen were fractures of both tibia and fibula (60 %), seventeen of which were located at the typical place already described 8—10 mm from the proximal end. Three of the fractures were of the radius, three of the ulna, four of the humerus, and two of the proximal metaphysis of the tibia just below the epiphysis. In two cases dislocation of the epiphysis was observed. Dislocation of the fractured bone ends was usual.

Complete healing of the fractures usually took place in all cases where the rats did not die from hypervitaminosis A, just as quickly as healing of artificial fractures produced in healthy rats for comparison. There was marked formation of callus, perhaps more pronounced than in normal rats, and the newly formed bone appeared thick and dense as judged by roentgenograms. The fractured bones often healed in wrong positions resulting in marked bone deformities (see illustrations: 4, 5, 25 and 32).

As judged by the roentgenograms it appears as if there is no lack of calcium in the bones. In fact there appears to be abnormal richness of calcium in some cases of the metaphyses, but no signs of osteoporosis.

The average *vitamin A content in the livers* of the rats in the various groups in the present experiment is compared in Table 15.

From these observations the approximate level of the vitamin A reserve in the liver associated with the symptoms of hypervitaminosis A could not be established, as the livers were not examined at the time

of the manifestation of the clinical symptoms, but at the conclusion of the whole experiment. The very high vitamin A reserve observed in some cases is thus explained by the fact that excess of vitamin A was given during a longer period than in those cases where the lower level of the vitamin A reserve was found.

Compared with the vitamin A content of the bear liver, these figures show, however, that hypervitaminosis A occurs in rats long before the vitamin A content per gram liver has reached the level which may be considered normal for the polar bear.

A closer study of the condition of hypervitaminosis A is in progress, including a further investigation of the tendency to bleeding, the bone abnormalities and the adrenals in hypervitaminotic animals and will be subject to a later publication.

IV. Conclusion.

1. Ingestion of 0.5—0.6 gram polar bear liver daily proved toxic to rats in all cases. In two cases 0.5—0.7 gram polar bear liver daily proved lethal.
2. Polar bear liver containing all its vitamin A was invariably found to be toxic, while the same liver freed of its vitamin A was non-toxic. In rats, the symptoms caused by polar bear liver ingestion were identical with those caused by ingestion of equivalent amounts of the oil containing the vitamin A extracted from the same polar bear liver, while equivalent amounts of the polar bear liver oil, where the vitamin A had been destroyed, had no ill effect on rats. The toxic effect of polar bear liver oil was identical with that of purified vitamin A concentrate in the form of whale liver oil concentrate, when given in corresponding amounts with regard to the vitamin A content (approximately 300 I. U. vitamin A/g body weight). Furthermore, no symptoms other than those following polar bear liver oil — or purified vitamin A concentrate ingestion, were observed in any of the rats given polar bear liver. Finally, the symptoms increased with increasing doses of vitamin A.

   It is therefore concluded that the toxic substance in polar bear liver is identical with vitamin A, and that ingestion of large quantities of polar bear liver by rats leads to the condition called hypervitaminosis A.

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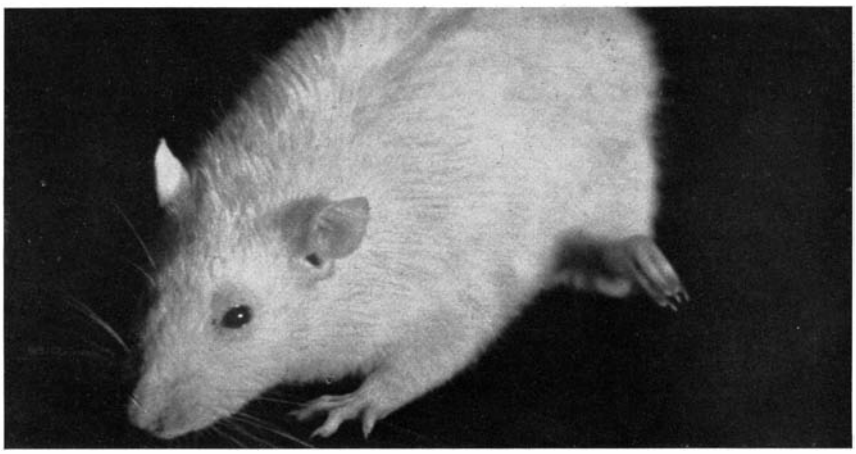
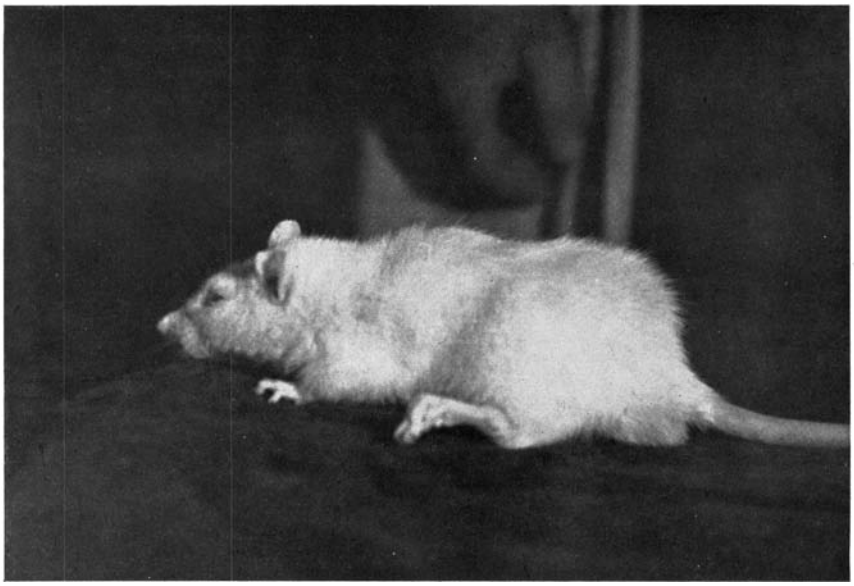
PLATES

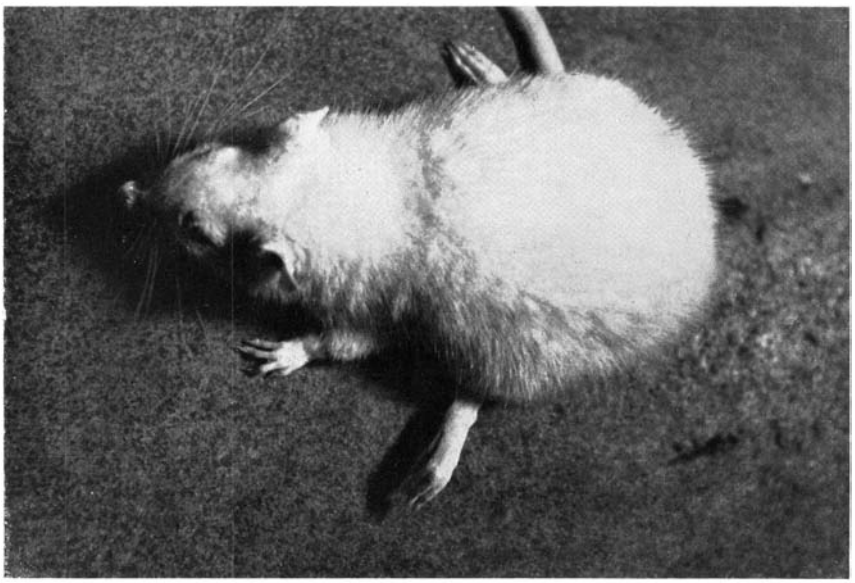


Ill. 1. Rat No. 2 in group given polar bear liver. — Exophthalmus and swelling of the palpebrae in rat given 0.6 g polar bear liver daily (see page 37).

Ill. 2. Rat No. 2 in group given polar bear liver. — Photograph taken four weeks after the polar bear liver had been removed from the diet, showing blood crusts around the eyes and disappearance of exophthalmus (see page 37).

Ill. 3. Rat No. 2 in group given polar bear liver. -- Photograph of rat given 0.6 g bear liver daily, taken 26 days after the beginning of the experiment. Fracture of left hind leg (see page 37).

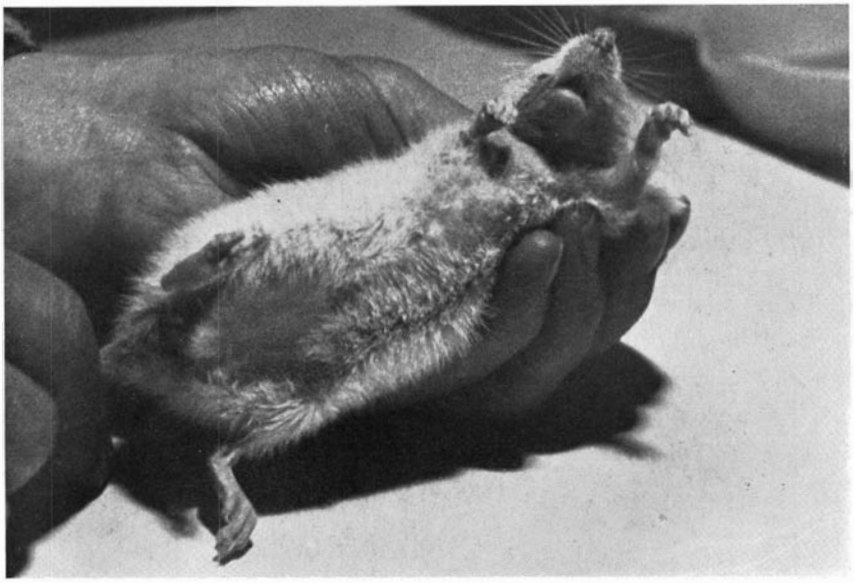




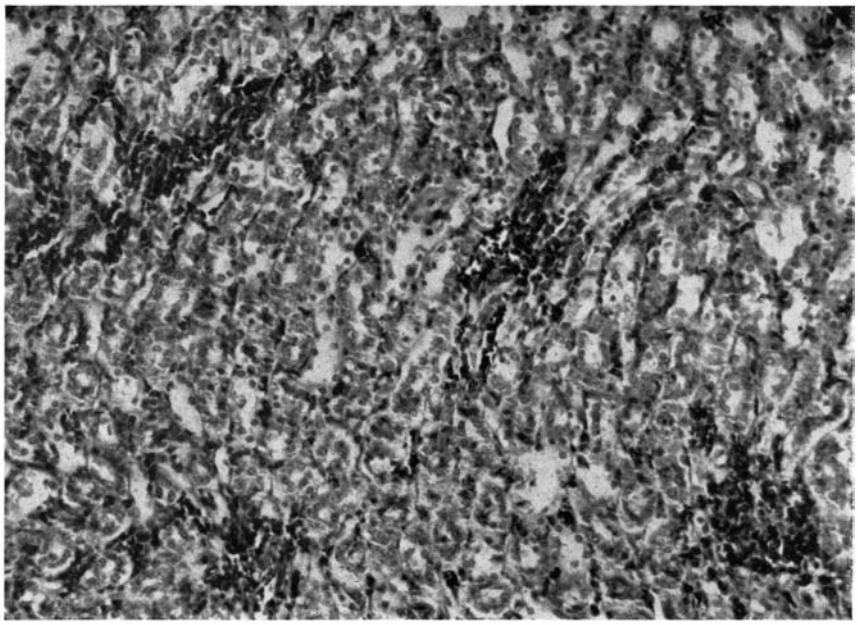
Ill. 4—5. Rat No. 2 in group given polar bear liver. — Photograph taken two weeks after the bear liver had been removed from the diet. Healing of the fractures of both hind legs and left fore leg in wrong position (see page 37).

Ill. 6. Rat given bear liver oil (340 I. U. vit. A/g body weight daily) during a period of 26 days, compared with control rat. The two rats had the same weight at the beginning of the experiment.

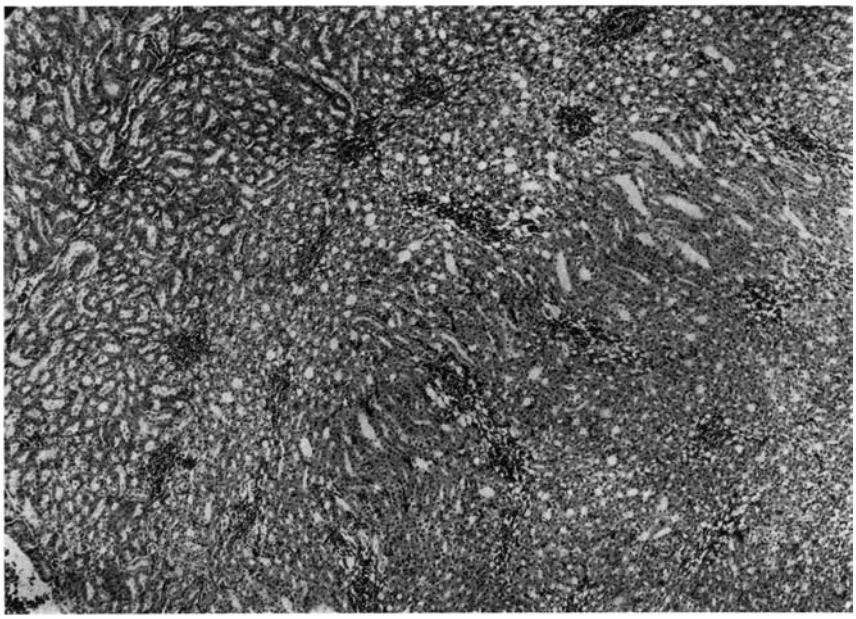
Ill. 7. Alopecia in rat given polar bear liver oil. (160 I. U. vit. A/g body weight daily.) (See page 48).



Ill. 8. Alopecia in rat given excess of vitamin A in the form of purified vitamin A concentrate during 23 days. (350—470 I. U. vit. A/g body weight daily.)
(See page 63).

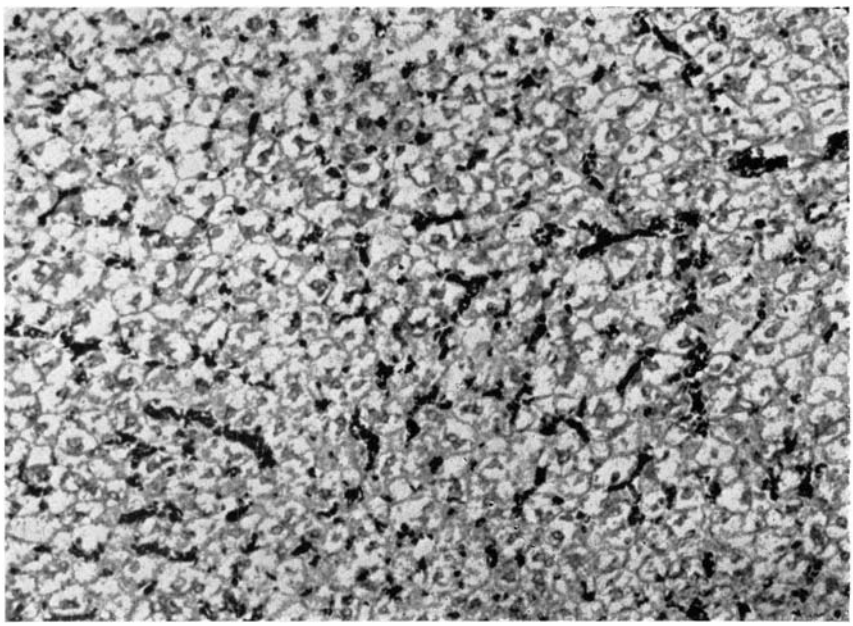


Ill. 9. Kidney from rat given 0.7 g polar bear liver daily during 16 days, showing hyperemia (see page 36). Hematoxylin-eosin staining. 200 ×.

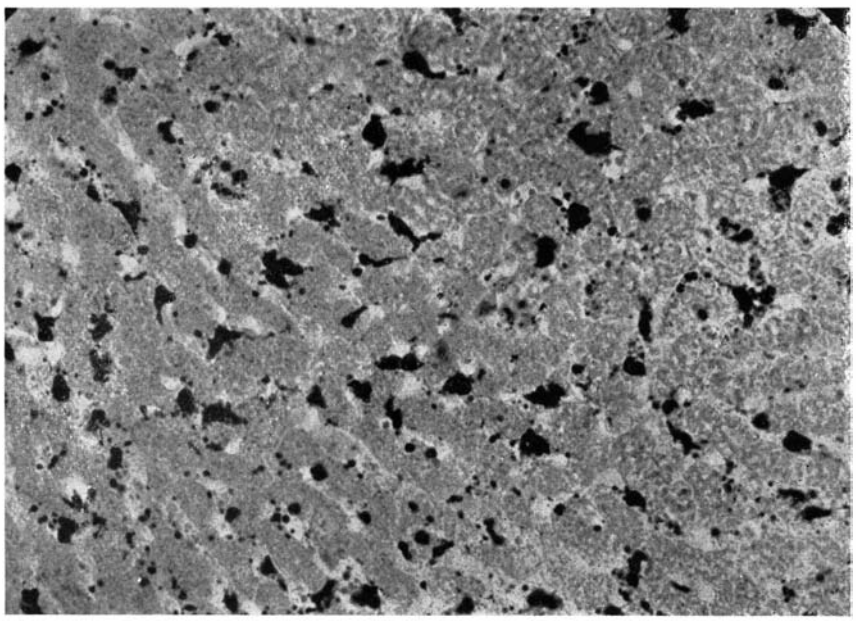


Ill. 10. Kidney from rat given polar bear liver oil, (428 I. U. vit. A/g body weight daily during 13 days), showing hyperemia (see page 48). Hematoxylin-eosin staining. 60 ×.

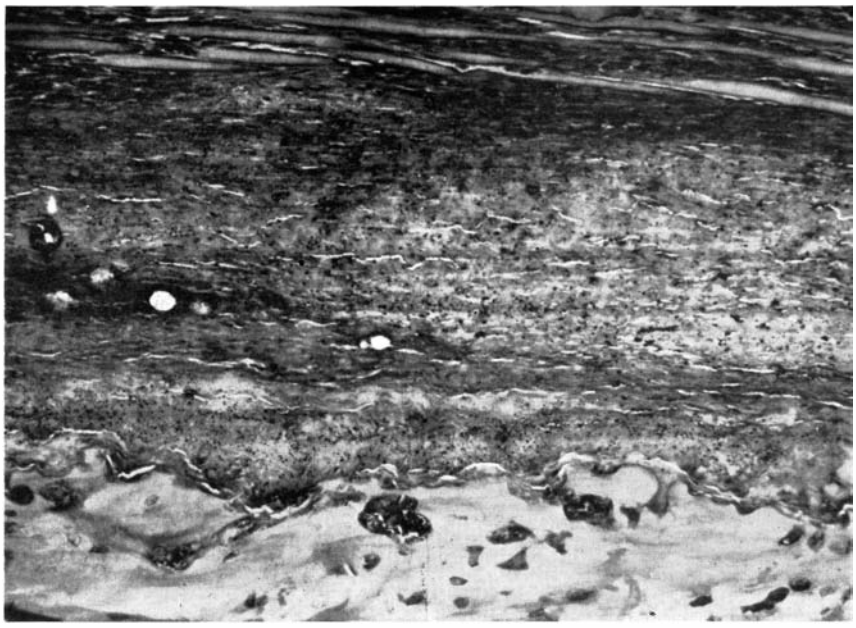
Pl. VI.



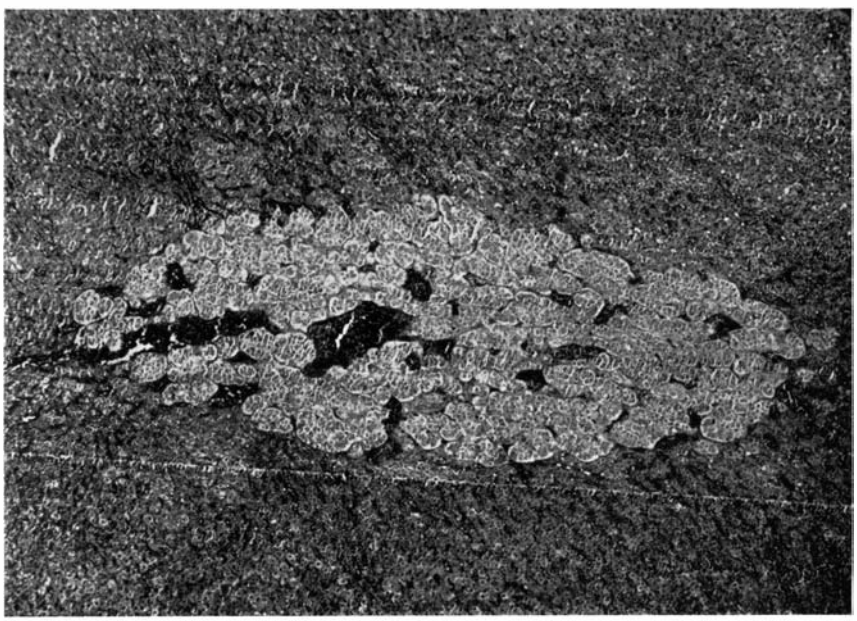
Ill. 11. Liver from rat given purified vitamin A concentrate (476 I.U. vit. A/g body weight daily during 34 days), showing large vacuoles in the liver cells, and hyperemia (see page 66). Hematoxylin-eosin staining. 200 ×.



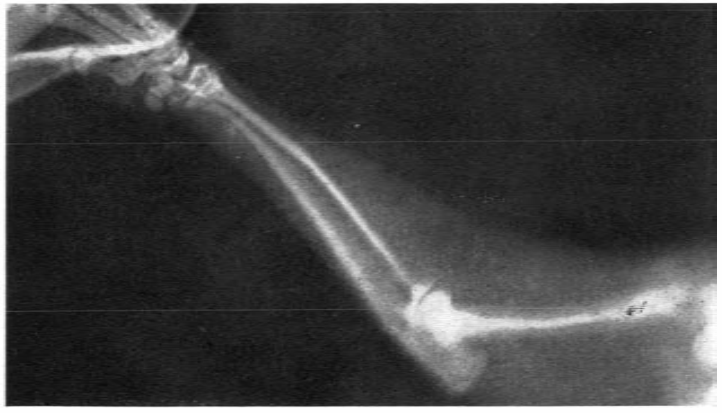
Ill. 12. Liver from rat given purified vitamin A concentrate (250 I. U. vit. A/g body weight daily) showing deposits of sudanophil droplets in, and in particular between, the liver cells. Sudan III staining. 240 ×.



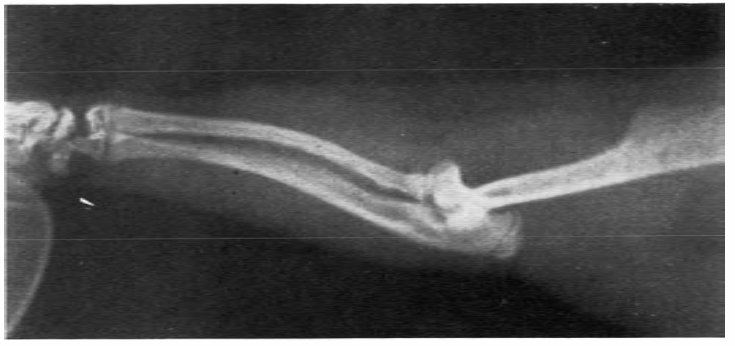
Ill. 13. The tibia from rat given polar bear liver oil (300—360 I. U. vit. A/g body weight daily during 24 days) showing old periostal hemorrhages (see page 53). Hematoxylin-eosin staining. 200 ×.



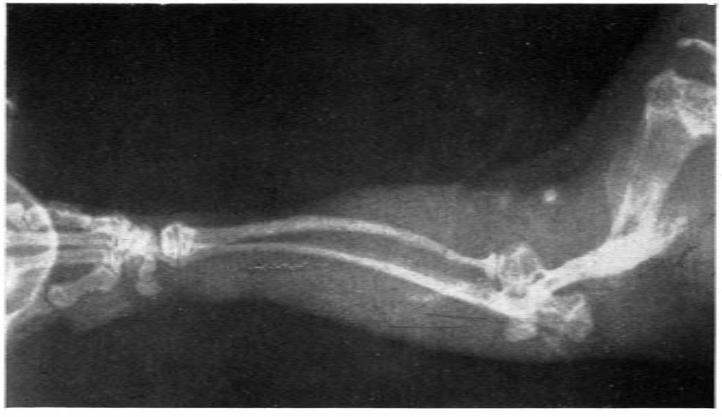
Ill. 14. Adrenal of rat given polar bear liver oil (250 I. U. vit. A/g body weight daily during 48 days), showing marked hyperemia within medulla. Hematoxylin-eosin staining. 60 ×.



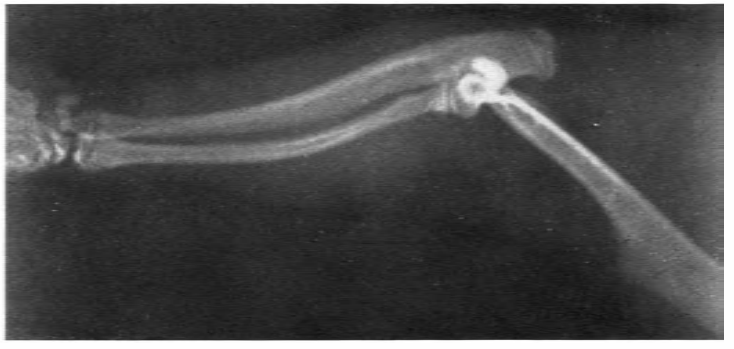
Ill. 17. Rat No. 1 in the group given polar bear liver (0.5 g daily). X-ray on the 60th day of the experiment of the right fore leg, showing thinning of the bone shafts and fracture of the ulna.



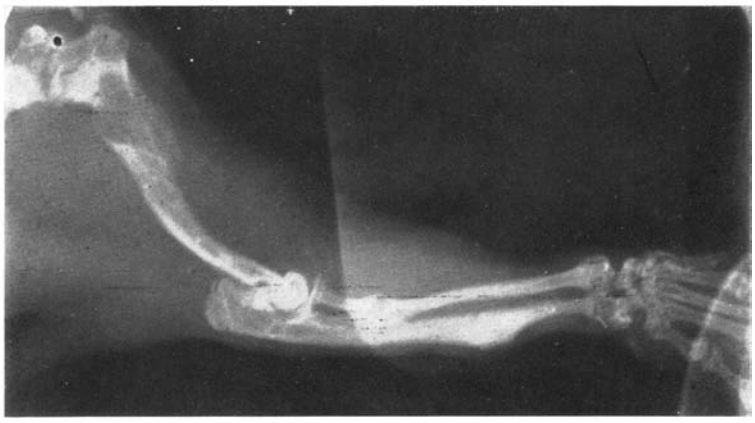
Ill. 15. X-ray of right fore leg of control rat after 30 days on normal diet (diet I).



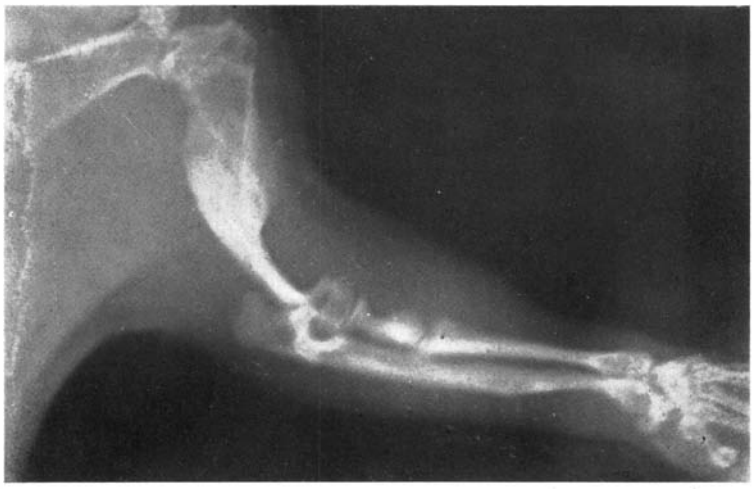
Ill. 18. Rat No. 2 in the group given polar bear liver (0.6 g daily). X-ray of right fore leg on the 44th day of the experiment, showing the abnormally thin bone shaft and fracture of the humerus.



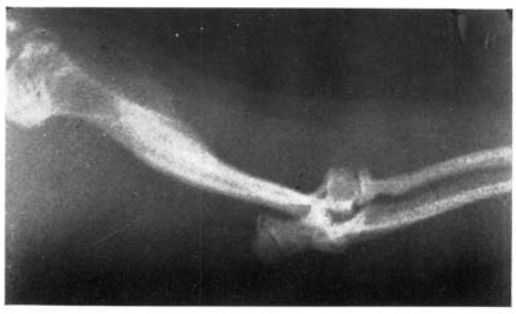
Ill. 16. X-ray of left fore leg of control rat after two months on normal diet (diet I).



a.



b.

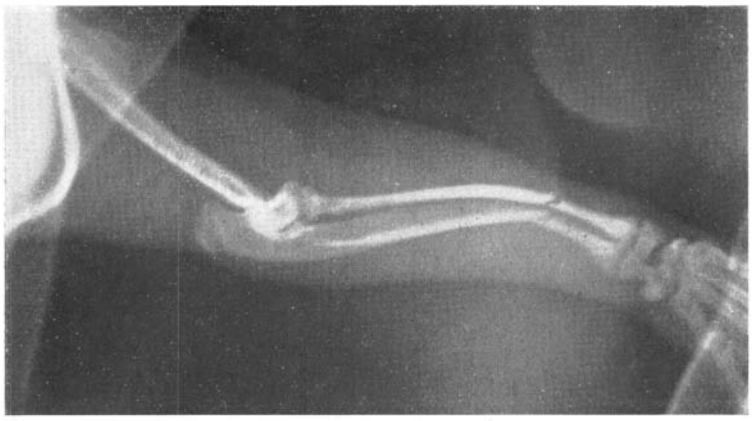


c.

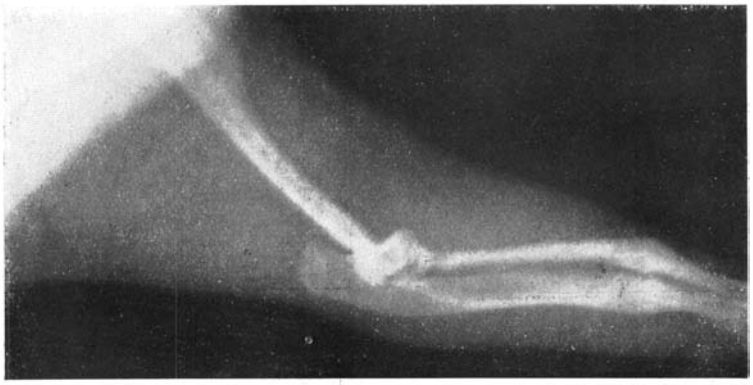
Ill. 19. Rat No. 2 in the group given polar bear liver (0.5 g daily). X-rays of left fore leg at the end of: 44 (a), 62 (b) and 94 (c) days of the experiment, showing healing of the fractures of the humerus, radius and ulna. The bear liver was removed from the diet on the 45th day of the experiments, at which time healing of the fractures was already in progress.

Pl. X.

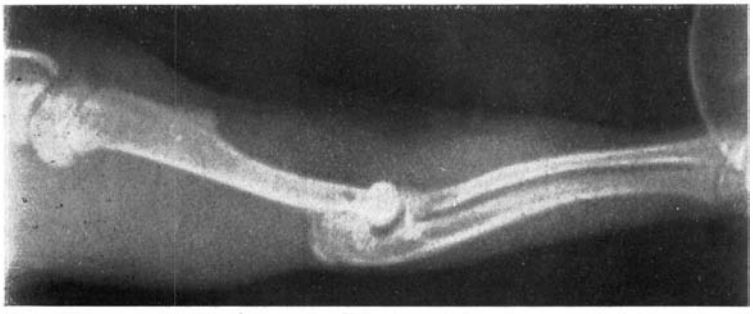
a



b.

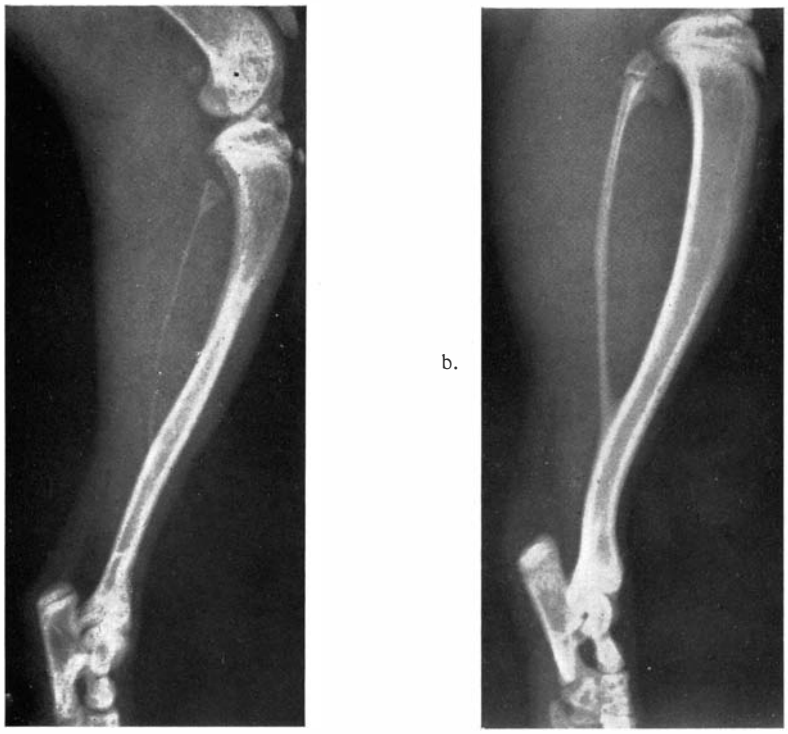


Ill. 20. Rat No. 3 in the group receiving polar bear liver (0.5 g daily).
a. X-ray at the end of 62 days of the experiment showing fracture of both radius and ulna.
b. X-ray 35 days later showing healing of the fractures with excessive callus formation despite the bear liver being given continuously in unchanged doses.



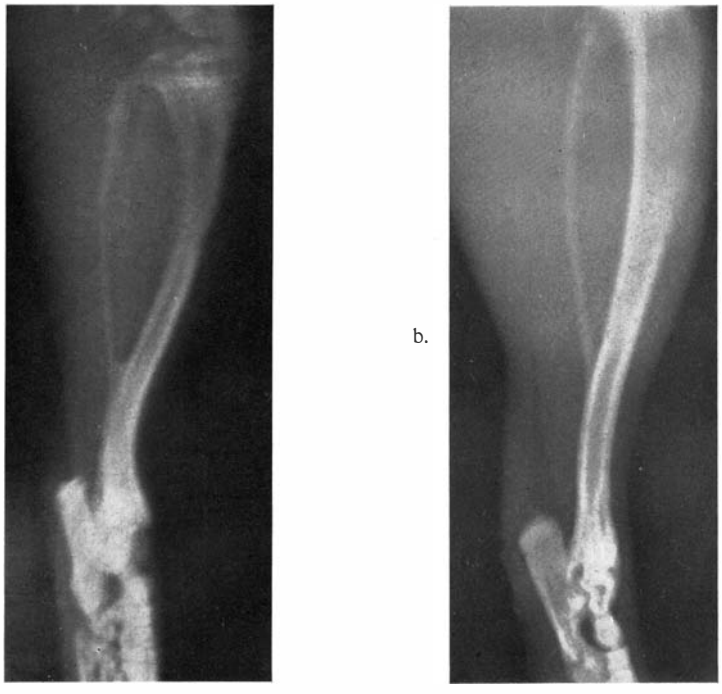
Ill. 21. X-ray on the 25th day of the experiment showing normal conditions of fore leg in rat receiving polar bear liver freed of vitamin A.

a. b.



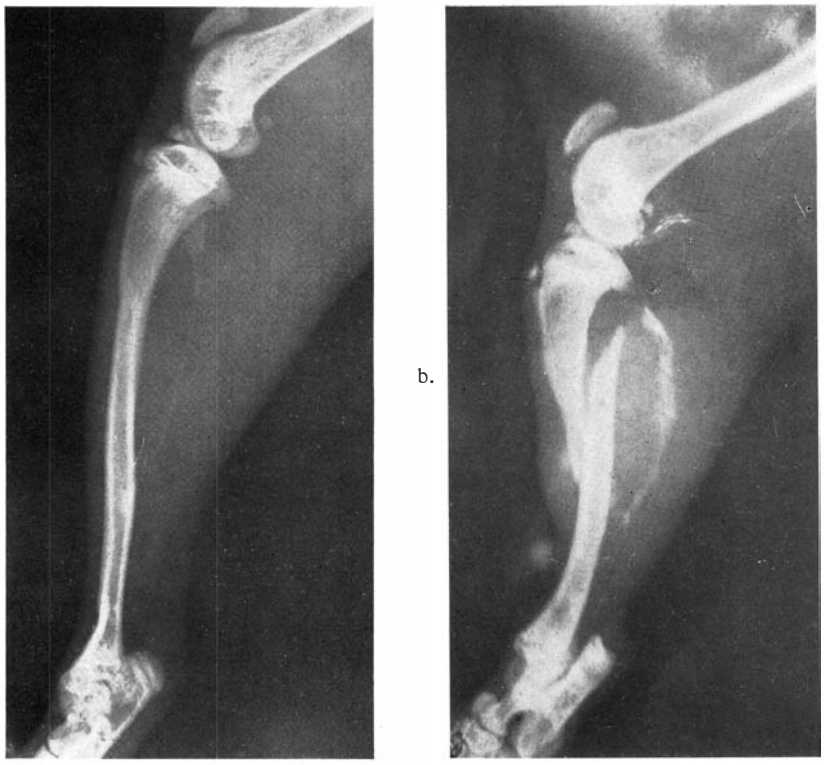
Ill. 22. a. Rat No. 1 in group given polar bear liver (0.5 g daily). X-ray on the 44th day of the experiment, showing abnormally thin bone shafts (see page 36).
b. Normal control rat.

a. b.



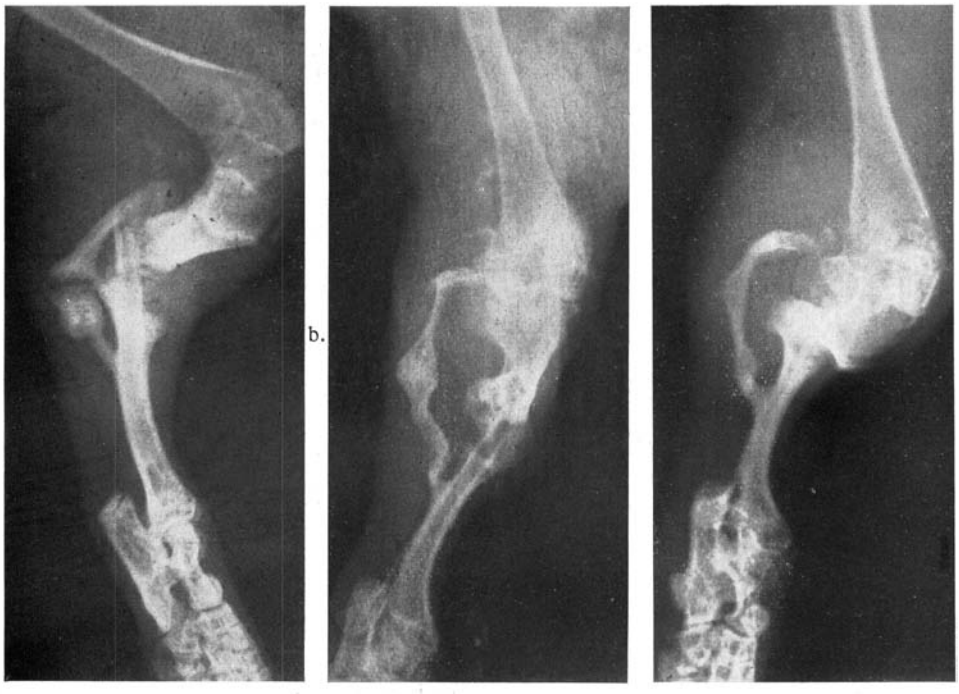
Ill. 23. a. Rat No. 5 in the group given polar bear liver (0.5 g daily). X-ray at the end of 62 days showing thinning of the bone shafts, compared with X-ray of —
b. rat given the same bear liver freed of vitamin A, taken simultaneously.

a. b.

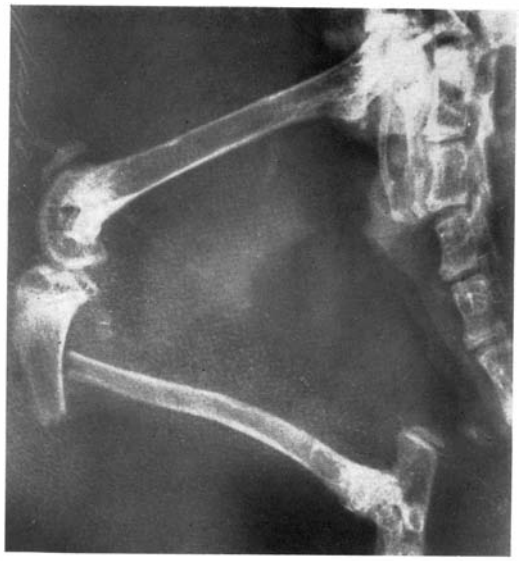


Ill. 24. Rat No. 1 in the group receiving polar bear liver (0.5 daily).
a. X-ray of right hind leg on the 44th day of the experiment showing thinning of the bone shaft.
b. X-ray of the same leg 16 days later showing fracture of the tibia and fibula.

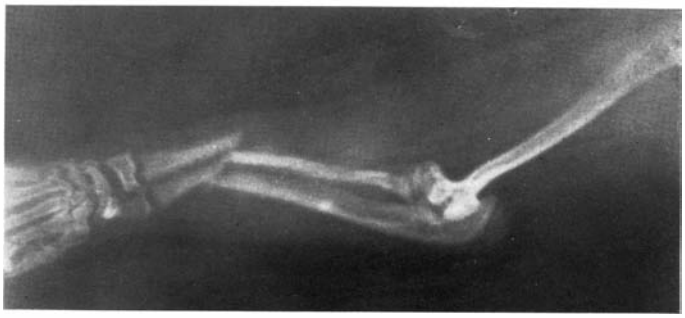
a. b. c.



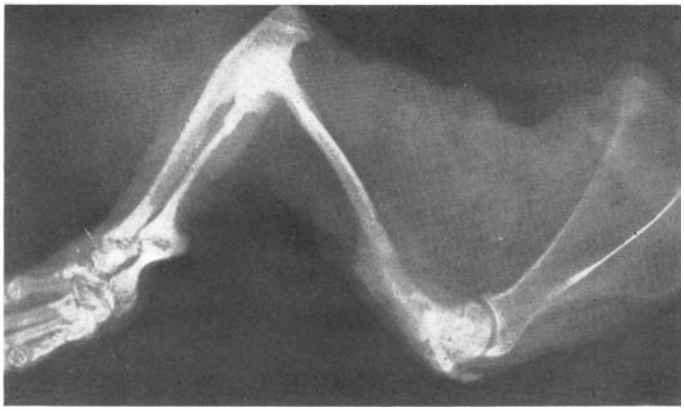
Ill. 25. Rat No. 2 in the group given polar bear liver (0.5 g daily). Left hind leg.
a. X-ray at the end of 30 days, b. at the end of 44 days, c. at the end of 62 days.
Healing of the fractures in wrong position with excessive callus formation is seen.
The bear liver was removed from the diet on the 45th day of the experiment,
at which time healing of the fractures was already in progress.



Ill. 26. Rat No. 4 in the group receiving polar bear liver (0.7 g daily). X-ray of the right hind leg at the end of 16 days showing fracture of both tibia and fibula.



a.



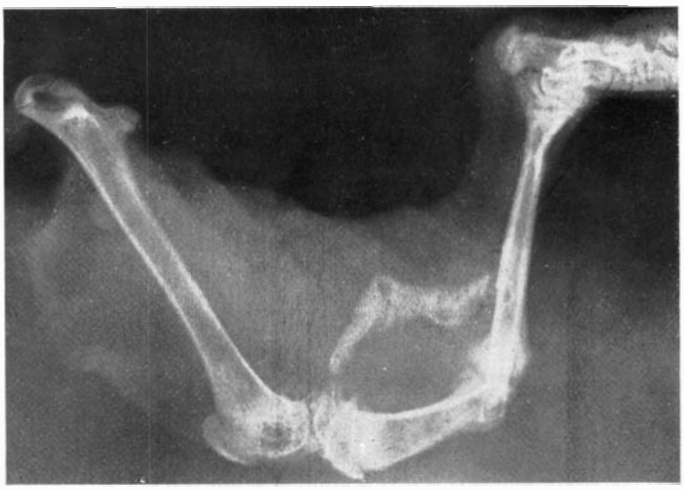
b.

Ill. 27. Rat No. 4 in group receiving polar bear liver oil (Exp. 3), 360 I.U. vit. A/g body weight daily.

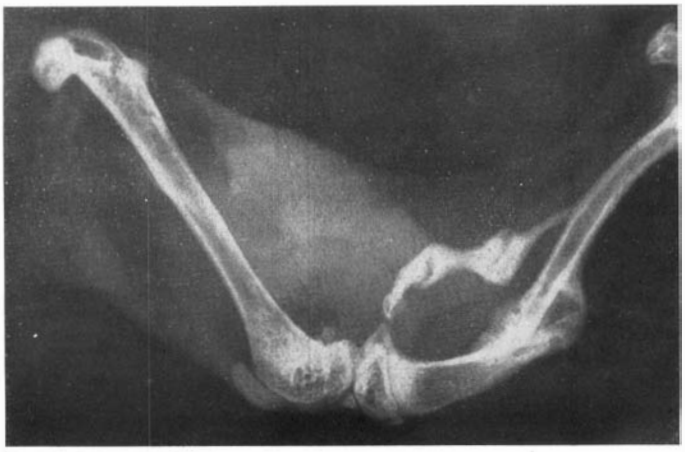
a. X-ray of left fore leg on the 25th day of the experiment showing fracture of the distal end of the radius and ulna.

b. X-ray of the same leg 19 days later, showing healing of the fractures with excessive callus formation, despite the bear liver oil having been given continuously in unchanged doses. The bone shafts are abnormally thin.

Pl. XIV.

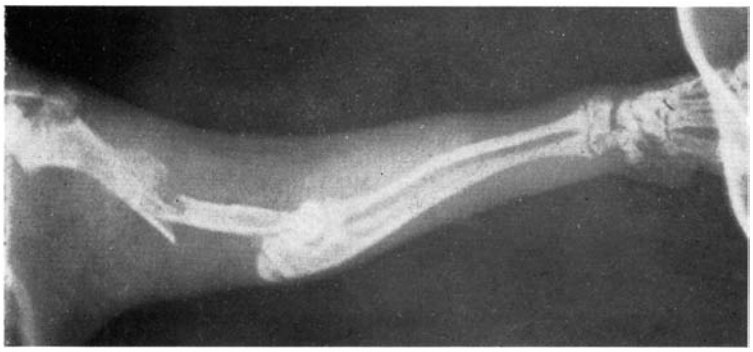


Left.

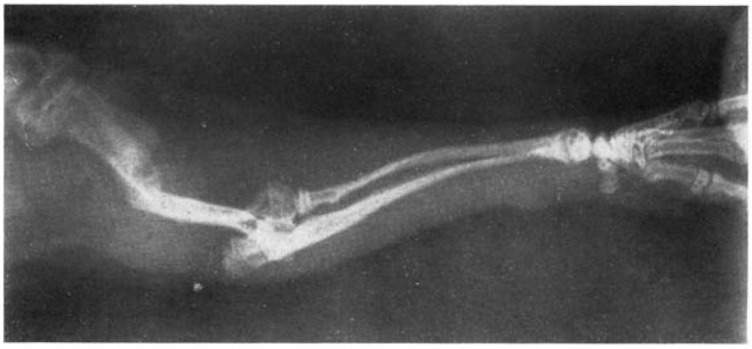


Right.

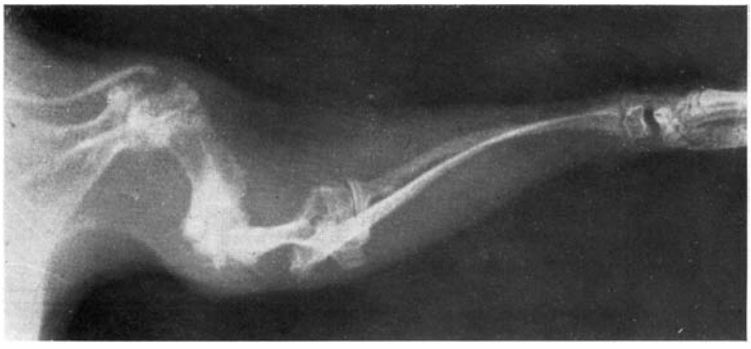
Ill. 28. Rat No. 4 in group receiving polar bear liver oil (Exp. 3), 360 I. U. vit. A/g body weight daily. X-rays of both hind legs on the 44th day of the experiment, showing fractures of both tibia and fibula with excessive callus formation.



a.



b.



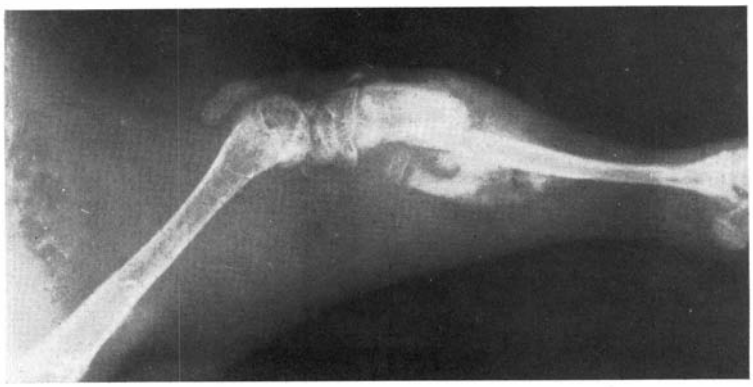
c.

Ill. 29. Rat No. 1 in the group receiving purified vitamin A concentrate (350—470 I. U. vit. A/g body weight daily). Left fore leg.

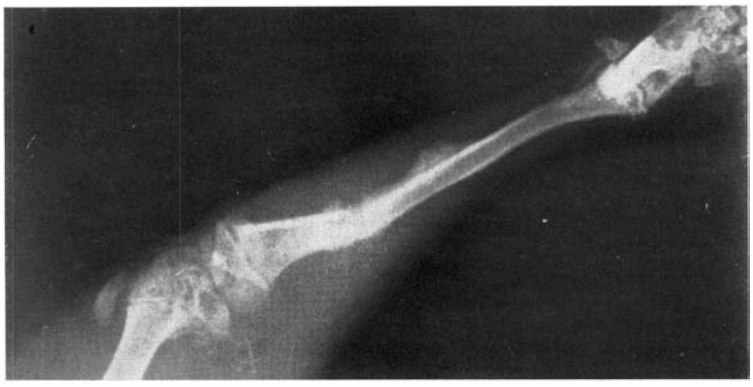
a. 20th day of the experiment.
b. 25th day of the experiment.
c. 30th day of the experiment.

Showing fracture of the humerus and a gradually increasing thinning of the bone shafts.

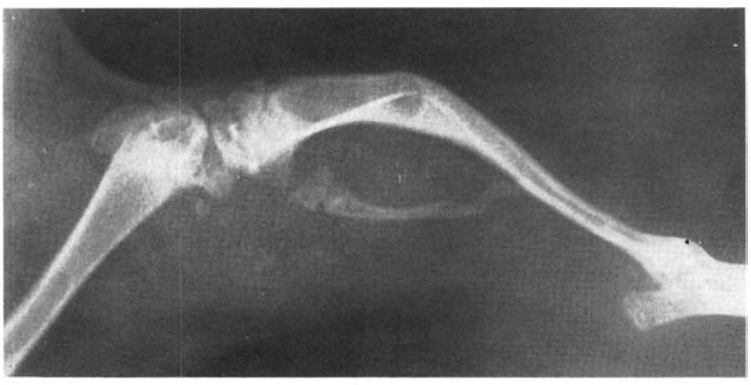
Pl. XVI.



Ill. 30. Rat No. 1 in the group receiving purified vitamin A concentrate (350—470 I. U. vit. A/g body weight daily). X-ray on the 30th day of the experiment showing fracture of the left tibia and fibula.

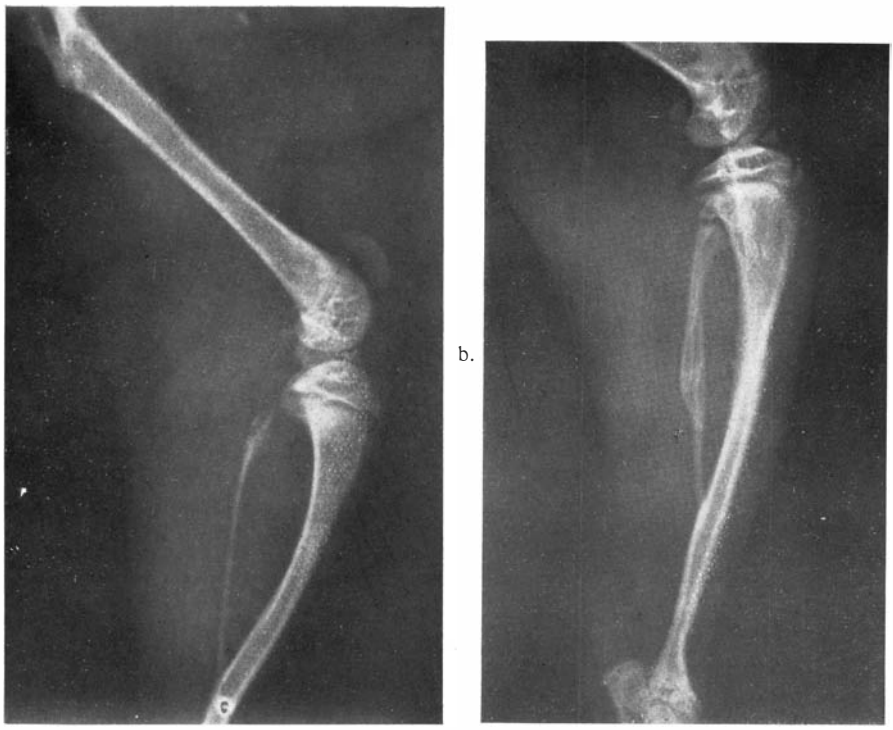


Ill. 31. Rat No. 1 in the group receiving purified vitamin A concentrate (350—470 I. U. vit. A/g body weight daily). X-ray of right hind leg on the 30th day of the experiment showing fractured tibia and fibula with callus formation, in spite of the fact that the excess of vitamin A was given continuously in unchanged doses.

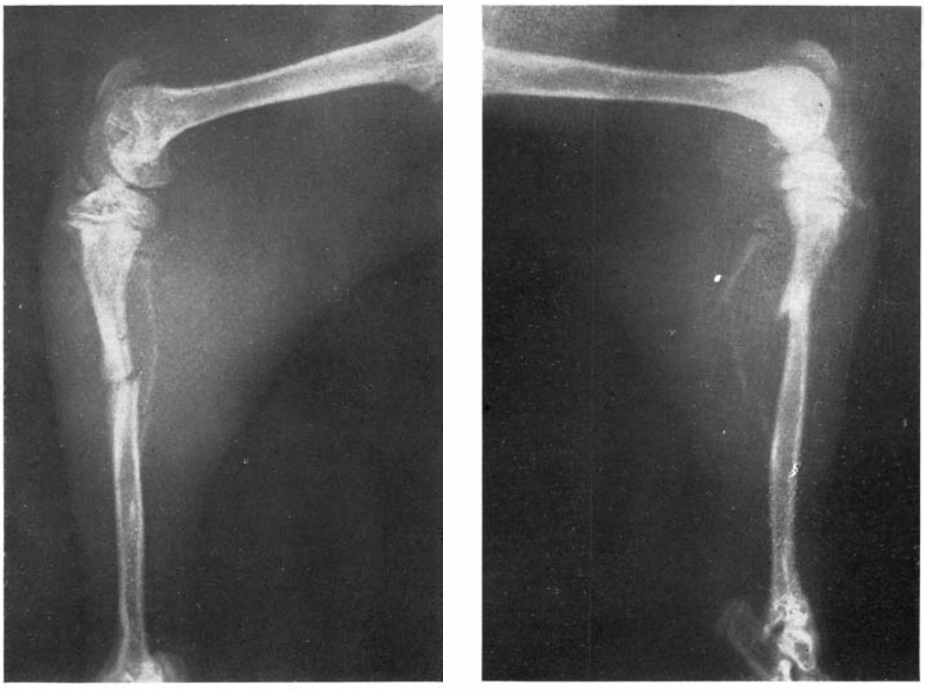


Ill. 32. Rat No. 2 in group receiving purified vitamin A concentrate (350—470 I. U. vit. A/g body weight daily). X-ray of left hind leg on the 44th day of the experiment showing healed fractures of the tibia and fibula, despite the excess of vitamin A being given continuously in unchanged doses.

a. b.

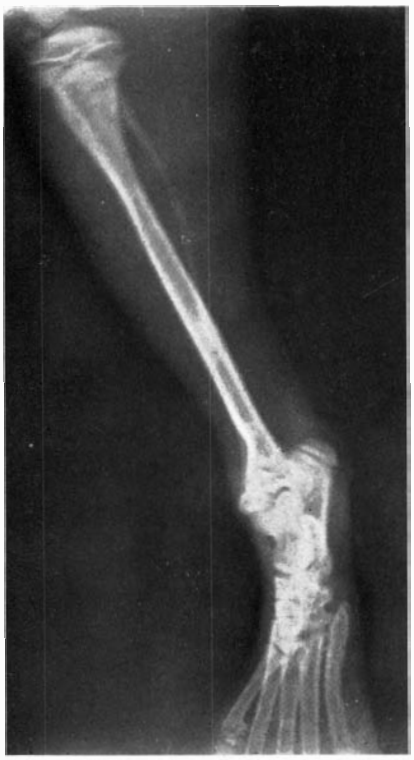


Ill. 33. Rat No. 4 in group receiving purified vitamin A concentrate (350—470 I. U. vit. A/g body weight daily).
a. X-ray of the left hind leg on the 30th day of the experiment showing the abnormally thin bone shafts.
b. X-ray of the same leg 14 days later showing fracture of the fibula with callus formation.

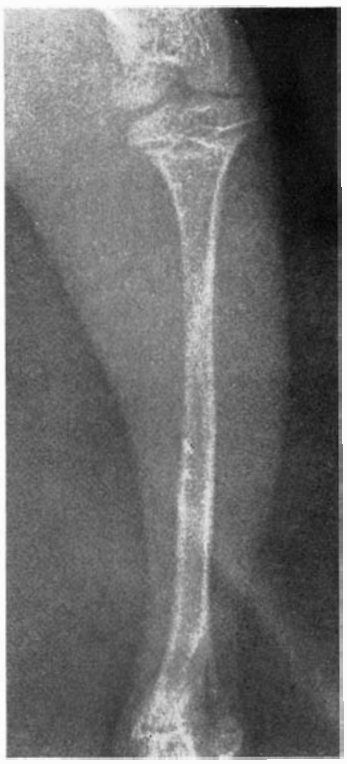


Ill. 34 Rat No. 5 in the group receiving purified vitamin A concentrate (350 – 470 I. U. vit. A/g body weight daily). X-rays of both hind legs at the end of one month of the experiment, showing the abnormally thin bone shafts and fractures of the tibia and fibula.

Pl. XVIII.



Ill. 35.



Ill. 36.

Ill. 35. Rat No. 3 in group receiving purified vitamin A concentrate (350—470 I. U. vit. A/g body weight daily). X-ray of right hind leg one month after the beginning of the experiment, showing a reduction in the diameter of the bone shafts, while the epiphyses appear unaffected.

Ill. 36. Rat No. 5 in the group receiving purified vitamin A concentrate (350—470 I. U. vit. A/g body weight daily). X-ray of the tibia showing the reduction in the diameter of the bone shaft, while the epiphysis appears to be unaffected.

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„ 38. LYNGE, B., *Lichens from Franz Josef Land.* 1931. Kr. 3,00.
„ 39. HANSSEN, O. and J. LID, *Flowering Plants of Franz Josef Land.* 1932. Kr. 3.50.
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„ 49. SCHAANNING, H. THO. L., 1. *A Contribution to the Bird Fauna of East-Greenland.* 2. *A Contribution to the Bird Fauna of Jan Mayen. — Zool. Res. Norw. Sc. Exp. to East-Greenland. I.* 1933. Kr. 3,00.
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„ 52. KIÆR, J. †, *The Downtonian and Devonian Vertebr. of Spitsb.* IV. Suborder *Cyathaspida.* 1932. Kr. 5,50.
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„ 56. DEVOLD, J. and P. F. SCHOLANDER, *Flowering Plants and Ferns of Southeast Greenland.* 1933. Kr. 20,00.
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„ 58. JELSTRUP, H. S., *Détermination astronomique à Sabine-Øya.* 1933. Kr. 2,50.
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„ 73. *Report on the Activities of Norges Svalbard- og Ishavs-undersøkelser 1927—1936.* 1937. Kr. 10,00.
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„ 82. NILSSON, TAGE, *The Downtonian and Devonian Vertebrates of Spitsbergen. VII. Order Antiarchi.* 1941. Kr. 11.50.
„ 83. HØEG, OVE ARBO, *The Downt. and Devonian Flora of Spitsbergen.* 1942. Kr. 33.00.
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„ 85. FØYN, SVEN and ANATOL HEINTZ, *The Downtonian and Devonian Vertebrates of Spitsbergen. VIII.* 1943. Kr. 5,00.
„ 86. *The Survey of Bjørnøya (Bear Island) 1922—1931.* Kr. 9,00.
„ 87. HADAČ, EMIL, *Die Gefäßpflanzen des „Sassengebietes" Vestspitsbergen.* Kr. 6.00.
„ 88. *Report on the Activities of Norges Svalbard- og Ishavs-undersøkelser 1936—1944.* Kr. 6,50.
„ 89. ORVIN, ANDERS K., *Bibliography of Literature about the Geology, Physical Geography, Useful Minerals, and Mining of Svalbard.* Kr. 12,00.
„ 90. HENIE, HANS, *Astronomical Observations on Hopen.* Kr. 3,00.
„ 91. RODAHL, KÅRE, *Vitamin Sources in Arctic Regions.* Kr. 6,00.
„ 92. RODAHL, KÅRE, *The Toxic Effect of Polar Bear Liver.* Kr. 12,50.

MAPS AND CHARTS

The following topographical maps and charts have been published separately:

Maps:

Bjørnøya. 1:25 000. 1925. New edition 1944. Kr. 3,00.
Bjørnøya. 1:10 000. [In six sheets.] 1925. Kr. 30,00.
Adventfjorden—Braganzavågen. 1:100 000. 1941. Kr. 2,00.
Svalbard. 1:2 000 000. 1937. New edition 1944. Kr. 1,00.
Topografisk kart over Svalbard. Blad C 13. Sørkapp. 1:100 000. 1947. Kr. 3,00.
Topografisk kart over Svalbard. Blad B 10. Van Mijenfjorden 1:100 000. 1948. Kr. 3,00.
Austgrønland. Eirik Raudes Land frå Sofiasund til Youngsund. 1:200 000. 1932. Kr. 2,00

Preliminary topographical maps [1:50 000] covering claims to land in Svalbard may be obtained separately.

Charts:

No. 501. Bjørnøya. 1:40 000. 1932. Kr. 4,00.
„ 502. Bjørnøyfarvatnet. 1:350 000. 1937. Kr. 4,00.
„ 503. Frå Bellsund til Forlandsrevet med Isfjorden. 1:200 000. 1932. Kr. 5,00.
„ 504. Frå Sørkapp til Bellsund. 1:200 000. 1938. Kr. 5,00.
„ 505. Norge—Svalbard, nordre blad. 1:750 000. 1933. Kr. 4,00.
„ 506. Norge—Svalbard, søre blad. 1:750 000. 1933. Kr. 4,00.
„ 507. Nordsvalbard. 1:600 000. 1934. Kr. 4,00.
„ 508. Kongsfjorden og Krossfjorden. 1:100 000. 1934. Kr. 4,00.
„ 509. Frå Storfjordrenna til Forlandsrevet med Isfjorden. 1:350 000. 1946. Kr. 4,00.
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„ 511. Austgrønland, frå Liverpoolkysten til Store Koldeweyøya. 1:600000. 1937. Kr. 4,00.

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