

hexose-diphosphoric acid, and to Harden and Young we owe the conception of the co-ferment as a substance comprising both the phosphate radical and an organic residue of unknown structure capable of passing on the phosphate radical to the sugar molecule.

In temperament the two colleagues differed greatly, Young's enthusiastic nature contrasting with the reserve and caution which were characteristic of Harden. Young was an active partner in the work and certainly played no inconsiderable part in its development.

In 1912, a new Institute of Tropical Medicine had been established at Townsville, Australia, and a selection Committee was appointed in London under the Chairmanship of Dr C. J. M. Martin to appoint certain members of the Staff of the new Institute. Young was chosen as the Biochemist, and in 1912 Dr and Mrs Young with their daughter Sylvia left London to make a new home in Australia. Whilst at Townsville, Young took up the question of the alteration in metabolism produced by residence in the tropics, and some new observations were recorded in a series of papers published between 1915 and 1920, chiefly in the *Annals of Tropical Medicine and Parasitology*. In 1919, in collaboration with Dr Breuil, pathologist at the Institute, an interesting paper on Tropical Australia and its Settlement was written and appeared in the *Medical Journal of Australia*.

Chiefly owing to the exertions of Prof. W. A. Osborne, who had just left Townsville to take up

the Chair of Physiology at Melbourne University, a Lectureship in Biochemistry was established at that University and offered to Young: somewhat later a Chair in Biochemistry was founded to which Young succeeded.

In Melbourne, Young's time was chiefly devoted to teaching; he was responsible for the instruction in this subject of students in the faculties of agriculture, dentistry, medicine, science and veterinary science; he built up a fine department, and in it were also carried out various investigations for the Government, two of especial interest dealing with the storage of fruit and the ripening of bananas.

Young was a man interested in many aspects of life. He was widely read in English literature, with a good knowledge of the drama of the Elizabethan age; he was also an expert but entirely self-taught cabinet maker. Whilst at the Lister Institute, he took up golf with his usual zeal and was to be found on summer evenings assiduously practising at Wimbledon Park. His colleagues at the Lister Institute remember him as an excellent friend, always good-tempered, interested in everything, and generally ready to argue on either side of the topic under discussion.

Within a period of two years the Biochemical Society has to mourn the loss of Harden, Robison and Young, the three men who did so much to unravel the mysteries of carbohydrate chemistry and to throw open this fruitful field to later investigations.

I. S.-M.

## The Vitamin A Content and Toxicity of Bear and Seal Liver

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(Received 23 October 1942)

It has long been known among Eskimos and arctic travellers that the ingestion of polar-bear liver by men and dogs causes severe illness. It has also been reported that the liver of a certain seal (*Phoca barbata*) is poisonous, although opinion on this point is less unanimous.

Richardson [1861] recounts that when members of an expedition led by Barentzoon to Novaya Zembla in 1596 ate bear liver they all became ill. In three cases the illness was severe, with loss of skin from head to foot. Another early account of the phenomenon was given by Kane [1856], who experimented with bear liver and found the incidence of the poisoning to be inconsistent. On two occasions the whole company on a journey became

sick after eating bear liver, but in other instances there were no ill effects. According to Koettlitz [1897], several members of an English expedition to Franz Josef Land, 1894-7, ate polar-bear liver and all suffered in consequence. Lindhard [1913] has also reported poisoning among members of another expedition. A bear was shot which, although thin, appeared to be healthy, and on the following day a stew was prepared from the liver, heart and kidneys. Although the heart and kidneys of bears had often been eaten without ill effects, the 19 men who partook of the stew all became sick. The first signs of distress occurred in two victims 2-4 hr. after the meal, and most of the others became ill during the night. The symptoms described

were drowsiness, sluggishness, irritability or irresistible desire to sleep, and severe headache and vomiting. During the second 24 hr. the skin of 10 out of 19 of the patients began to peel around the mouth, beginning in spots and gradually spreading over larger areas. In some cases the peeling was confined to the face, but in several it was general. Lindhard also described three other cases in which the skin peeled from head to foot after eating bear liver. The Norwegian explorer Nansen [1924] has mentioned that on two occasions he ate small amounts of bear liver without ill effects. It seems probable therefore that the poisonous effects only occur when large quantities are consumed. The most recent cases of poisoning have been described by Doutt [1940].

During a recent expedition made by one of us to north-east Greenland, 1939-40, specimens of polar-bear liver were collected with a view to identifying the toxic substance. On chemical and biological examination these specimens were found to be very rich in vitamin A, as also was a specimen of liver from *P. barbata*. It seems probable that this high concentration of vitamin A is the cause of toxicity, and that the ingestion of more than small amounts of liver leads to hypervitaminosis A.

#### METHODS

*Vitamin A estimations.* 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 [Moore, 1937]. The first bear liver to be examined was taken from a 2-year-old female and contained 18,000 i.u./g. of wet material. A second specimen was taken from a 4-year-old male, and also contained 18,000 i.u./g. From a third specimen a value of 13,000 i.u./g. was obtained. A single specimen of seal liver contained 13,000 i.u./g. In biological tests groups of rats were given the liver oils 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 weight increases observed were as follows:

	Calculated daily dose i.u.	Mean wt. increase in 28 days (g.)	Approx. i.u./g. liver by biol. test
Seal-liver oil	2.6	25	14,000
( <i>Phoca barbata</i> )	10.3	48	12,000
Bear-liver oil (no. 1)	2.6	29	26,000
( <i>Ursus maritimus</i> )	10.3	56	24,000
Carotene	2.6	23	—
	10.3	47	—

Since only a few rats were used (usually 3 males per group) these results do not allow accurate independent estimates to be made of the vitamin A contents of the livers. It is obvious, however, that they agree with the high contents found by the  $SbCl_3$  method.

*Tests for toxicity.* According to Jackson [1899], V. Harley, of University College, London, examined bear liver in order to find the reason of its toxicity. Intraperitoneal 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 3 days after subcutaneous inoculation with an ethereal extract, but the result was possibly accidental. Mice were unaffected by injections of alcoholic and aqueous extracts.

The very high content of vitamin A in the liver suggested that it might give rise to hypervitaminosis A if eaten in more than small amounts. This condition was first described by Takahashi, Nakamiya, Kawakimi & Kitasato [1925], and has since been investigated by many workers. Although it is not quite certain that vitamin A itself is poisonous, the toxicity is at least closely associated with the vitamin in its concentrates. In our laboratory the lesions produced have varied remarkably according to the size of the rat and the magnitude and duration of the overdosage. 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 softening and fracturing of the bones, seen most frequently in growing rats, and profuse and sudden internal haemorrhage, often seen in adult animals. In one series of experiments a dose of 30,000 i.u. vitamin A daily in the form of halibut-liver oil was found to be definitely excessive for rats of about 200 g. body weight, invariably causing roughening of the skin, and occasionally death through haemorrhage.

The liver tested for toxicity in the present experiments was from the 2-year-old female bear. Although a value of 18,000 i.u. of vitamin A/g. had originally been obtained the portions now tested contained only 10,000 i.u./g. Carefully planned tests were difficult because of the reluctance of the rats to eat the liver. We have observed the same disinclination in rats when given the livers of other rats which had been allowed to accumulate very high reserves of vitamin A. One rat ate a total of 33.1 g. of the bear liver during a period of 22 days, an amount containing an average of 15,000 i.u. of vitamin A/day. It became anaemic and the hind legs were paralysed. When moribund it was killed.

At autopsy, the profuse internal haemorrhage typical of hypervitaminosis A was found, particularly under the skin, but also in the pericardium. Another rat ate 5.3 g. of liver during a period of 9 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. Another rat ate 24 g. of liver in 22 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, were readily consumed without ill effects, in amounts corresponding to 1-2 g. 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. It is probable that the absence of ill effects was due to the refusal of the animals to accept the liver in amounts sufficient to poison them.

#### DISCUSSION

It is questionable what factor should be taken to convert doses used for rats to the corresponding doses for man, but the ratio of 75 taken from the relative food intakes of the 100 g. rat and 70 kg. man would seem reasonable. If we take 100,000 i.u. of vitamin A as sufficient to cause immediate illness in the rat, then about 7,500,000 units should cause illness in man. This amount would be present in 375 g. of bear liver containing 20,000 i.u. of vitamin A/g., not an excessive portion to be eaten at a single meal.

Some years ago Mr J. F. Ward of the Crookes Laboratories mentioned to one of us a case of presumed poisoning through excessive halibut-liver oil consumption, which may be of interest in the present connexion. One of the men engaged in the manufacture of the oil took, without instruction, 4-5 oz. daily. After 5 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.

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. If bear liver is toxic to the rat for any reason other than its high content of vitamin A, therefore, the amounts which must be eaten to cause poisoning must be so large as to render the animal liable to concurrent hypervitaminosis A. As far as can be concluded from experiments with rats, which may of course differ widely from man in their toleration of toxic substances, there seems 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 be unlikely to be rich in vitamin A. There would seem to be no objection to the use of preparations made from bear-liver oil as sources of vitamin A in therapeutic doses.

#### SUMMARY

1. Specimens of the livers of the polar bear and the seal, *Phoca barbata*, were found to be very rich in vitamin A. Three specimens of bear liver contained 18,000, 18,000 and 13,000 i.u./g. respectively of wet material. A specimen of the seal liver contained 13,000 i.u./g.

2. The ingestion of excessive amounts of bear liver by rats led in one instance to fatal hypervitaminosis A. Other rats which ate slightly smaller amounts of liver showed no obvious sign of injury. The well-known poisonous action of bear liver in man is probably due to its high content of vitamin A.

Our thanks are due to Dr Vernon Booth and Mr Alan Davies for help in parts of the work, to Dr L. J. Harris for his valuable criticism, and to the Scott Polar Research Institute for library facilities. One of us (K. R.) is indebted to the Nansenfondet, Oslo, Freiafondet, Oslo, and Varekrigs Forskningsfond, Oslo.

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