International Council for
the Exploration of the Sea

C.M. 1971/E:5
Fisheries Improvement Committee

Zinc and the Etiology of Cancer

by

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Summary

The amounts of several metals are especially high in special areas of estuaries of the North Sea. The Greater London Council has published the following values for heavy carcinogenic metals: zinc, 2390-5860 mg/kg; nickel, 150-350 mg/kg, and cadmium, 30-70 mg/kg. The values are calculated on a dry weight basis. This is why the North Sea estuaries provide quite ideal experimental fields for cancer research.

Halme, De Szilvay, Dvizikov et al., Halme et al., McQuitty et al. have only recently finally proved that zinc is a very cancerogenic substance, perhaps the most dangerous of all substances causing cancer. That excess zinc increases and, on the other hand, small quantities decrease cancer, is the most important achievement of the examinations mentioned above. This result may be of great importance for the whole cancer problem. At the moment, cancer is not yet a solved problem. Cancer research is the most demanding field that the biological sciences have been involved in, the problems in this research being so extensive and complicated. Therefore, also e.g. the zinc examinations mentioned above on seawater estuaries must urgently be started on a much larger scale than has been done so far.

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As can be seen from the paper by R. G. J. Shelton (1970), Fisheries Laboratory, Burnham-on-Crouch, Essex, the amounts of several metals are especially high in certain areas of the estuaries of the North Sea. Recent analyses e.g. by the Greater London Council, gave the following values for heavy metals: zinc 2390-5860 mg/kg; copper, 505-2500 mg/kg; chromium, 200-1065 mg/kg; nickel, 150-350 mg/kg and cadmium, 30-70 mg/kg. All values are calculated on a dry weight basis.

Among the metals, mainly zinc, cadmium, cobalt, and nickel are highly carcinogenic, others are less cancerous. Especially zinc, which is a very common and widely distributed carcinogenic metal, is very dangerous, as has been decisively proved only recently. It is to be noted that this metal is very common in various foodstuffs, in the drinking waters, in the painting-stuffs, etc.

The International Study of Pollution of the North Sea and its Effects on Living Resources and their Exploitation would give an excellent possibility at the same time to study the danger-amounts of these metals to the fish and other sea-animals of the polluted areas, compared with the clean waters. Particularly to the Zn-question this comprehensive and thorough study would be very important.

On the basis of ten years' experiments the author established that zinc - contrary to earlier opinions - is a slow but especially strong carcinogene (Halme, 1960). Professor Gyula De Szilvay (Semmelweis Institute, Bremen) has then after three years' work been able to experimentally confirm (1963) most of the results discovered in my investigations. Later also Dvizikov et al. (1968, 1970) have, independently from these investigations, noticed the strong carcinogenic effect of zinc. Thus four investigators in Finland, West Germany and the Soviet Union have come to the same

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result that zinc is a threatening carcinogenic substance. Also my later works (1968, 1970a, 1970b) and Halme et al. (1969) have now proved this. McQuitty et al. (1970) discovered inhibition of tumor growth by zinc deficiency. This group of seven men noticed that tumor growth decreased markedly in the zinc-deficient group, compared with the control series. Thus, also this study demonstrated the importance and necessity of zinc for neoplasms.

On the basis of these tests it can be concluded that excessive amounts increase, insufficient amounts decrease, the number of tumors, which clearly indicated that zinc is an essential factor for the development of cancer. Though there is not yet evidence of zinc being the most important inducer of cancer - which is quite possible - the observations mentioned above, among other things, urge that zinc investigations be urgently started on a very much larger scale that has been done so far. Then, above all, consideration must also be given to other carcinogenic metals, tryptophan and its metabolites, the code system in the cell nucleus, and tautomerization and ionization of the hydrogen. In addition, as to water circumstances, which lack most carcinogenes, also the relatively common occurrence of tumors produced by viruses and chemical substances must be considered.

It can be estimated that on average a man in densely populated areas takes in by different ways 20-100 mg Zn in a day. Tests have shown that 5-20 mg Zn added to the zinc in normal food and drink, produces cancer. There is a certain zinc level independent of the differences in metabolism. This in mice is about 40 mg Zn as a tissue value (the tests are based on the zinc content of 65 mice burnt whole, 1966). The excretion of zinc by cancer patients is also much less than that of healthy people. Thus the points are very important and urge the zinc problem - and the whole problem of metals as well - to be considered in different research institutes immediately and thoroughly.

The most important achievement of this investigation, and, in this connection, most essential, is that excessive amounts of zinc increase cancer and that amounts of zinc as low as possible decrease cancer. When zinc is eliminated from the food and drink of man as carefully as possible - sufficient amounts of zinc still remain for the use of the body (e.g. carbonic anhydrase) - the present great cancer frequency can be greatly decreased. A marked change can be achieved even by eliminating zinc from drinking water and leaving out from the daily diet the food-stuffs with high zinc concentration.

In the book "Fish in Research", edited by Otto W. Neuhaus et al. (1969) and in the earlier "Neoplasia in Cold-Blooded Vertebrates", written by Balduin Lucke et al. (1949) 393 references are summarised. According to the writers Wellings, Ashley, Scarpelli, Siperstein et al. and Tarr (1969) among other things the following observations can be made:-

1. The feeding of 1 part per billion of purified aflatoxin B_1 produced hepatomas in a high percentage of fish. This amount is surprisingly low.

2. Typical examples in fish are epithelioma at the lip and face in catfish and hog suckers, epidermal papilloma in pleuronectid fishes, and hepatoma in rainbow trout. The incidence of spontaneous neoplasms in teleosts is largely concentrated in five families: the salmonoids, cyprinoids, codfishes, flatfishes and flounders.

3. Once the disease was established in a particular pool, the incidence tended gradually to increase.

4. Environmental neoplasia can be analysed in the laboratory utilizing common species of freshwater aquarium fish. This suggests the presence of naturally occurring or human-generated carcinogenic agents.

5. Changes in ionic strength of the water markedly influenced the growth rate of the melanomas. The melanosis and tumor formation is associated with macromelanophores which are heritable as a dominant sex-linked factor.

6. There is a correlation between tumor incidence and low salinity. This is especially true in the instance of young starry flounder. Tumor incidence in these fish is in excess of 50% in some estuaries.

7. It is important that there are already strong indications that this "multiple factor hypothesis" of tumorigenesis is not only applicable to mammals, but also throughout the biological world.

8. In 1966 the U.S. Smithsonian Institution joined with the National Cancer Institute in establishing a Registry of tumors in lower animals. Its purpose: to collect specimens, the study of which will aid in gaining an understanding of neoplastic processes.

9. Comprehensive reviews of tumors of fishes, amphibians and reptiles have clearly established that lower vertebrates are commonly affected by neoplastic diseases, and that some of these are essentially identical in structures and biological behaviour to their counterparts in the higher vertebrates.

10. We have been trying to induce "functional" tumors in trout with aflatoxin but so far we have not been able to transplant the tumors or transmit the disease in spite of numerous attempts.

11. The high incidence of epitheliomas in certain species of fish suggests that genetic factors may play an important role in their induction. The increasing number of pollutants, and the extent of pollution of rivers and lakes and offshore oceans markedly increases the need for such studies.

The sites of varying reactivity in the DNA molecule are not difficult to imagine. They may arise from difference in the density of hydrogen bonds, depending on the nature of neighbouring residues, or even from a difference in chemical bond stability owing to the inductive effects of π-electrons belonging to closely situated bases. One can suppose that certain combinations of neighbouring bases give rise to "weak" spots which bear the brunt of attack by chemical mutagens (Bresler, 1971).

Birks (1961) has made an interesting addition to the growing number of theories concerning the carcinogenic capabilities of certain aromatic compounds. He proposes that a necessary, but not sufficient, condition that a compound be a primary carcinogen, is that its first single π-electron absorption band strongly overlaps the emission spectrum of tryptophan. This proposal followed his observation that for 22 of the 23 carcinogenic members of the polycyclic hydrocarbons and 1,2-benzanthrasene derivatives discussed by Schoental et al. (1949), the energy of the first exited π-singlet state lies between 3.04 and 3.20 eV. This suggested that the carcinogenic mechanism might involve an intermolecular resonance between some important cellular constituent and a carcinogen (Memory, 1962).

Evidence for energy transfer in DNA is the fact that the phosphorescence of native DNA is not the sum of the expected emission from individual nucleotides. Using electron spin resonance and optical emission it has been demonstrated that the emission is predominantly from thymine. A proton is removed from nitrogen-1 position of thymine. Since this proton is involved in the normal hydrogen bonding of thymine to adenine in DNA, it might be expected that this proton could be shifted to adenine with the expected thymine exitation in DNA. In summary, it is apparent that protons absorbed in either thymine or adenine in DNA can be equally effective in promoting thymine phosphorescence.

In general, enzymes responsible for oxidations that supply energy to the organisms utilize DPN^+, while those which catalyze reductive biosynthese employ TPN^+. Tumor tissues derive largely by anaerobic pathways of metabolism. Several DPN-dependent dehydrogenases are zinc-proteins. Beef liver glutamic acid dehydrogenase and the alcohol dehydrogenase of yeast, horse liver, and human liver contain 4, 4, 2, and 2 gram-atoms of zinc per mole of protein, respectively.

Also dimerization of CRM (cross-reacting material) sub-units has been found to be a zinc-activated bimolecular reaction. A detailed study of the conditions for producing enzymatically active protein from the U9-S33 inactive CRM's revealed that the reaction required the presence of a metal ion. Zinc as a molar ratio of metal ion/ protein of about 25:1 was the most active. Of the other cations tested only cobalt showed activity.

The mutant protein is much more sensitive to inhibition by zinc ion, and the energy of activated for tryptophan biosynthesis catalyzed by this mutant protein is much higher than the value obtained with the wild-type enzymes. Mutant enzymes differ from the wild-type protein and from one another in other ways: electrophoretic mobility, behaviour on column cromatography, and so on.

Perhaps the most striking difference so far found between tryptophan synthetase mutants relates to their ability to form a protein that is inactive enzymatically but has immunological properties similar to tryptophan synthetase. Those mutants that produce CRM are called CRM-positive (CRM^+) mutants; those that do not are termed CRM-negative (CRM^-) mutants (Hartman et al., 1969).

We now know enough about cancer to see that this extensive and complicated problem is the most exacting task that biological science - or to be more precise, biological sciences - has ever faced. For in cancer research are now involved all the known branches of science that have something to do with the living world. And as more information is gained, still new fundamental sciences get involved, which earlier were thought to have nothing to do with cancer.

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