FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIGS. 1-3.—Collections of crystals in Kupfer cells of rabbit. Hæmatoxylin and eosin $\times 250$. The slight cellular increase in the portal tract in fig. 3 is not related to the presence of dust.

FIG. 4.—Rat lung. Hæmatoxylin and eosin $\times 8$.

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 5.—Rat lung. Hæmatoxylin and eosin $\times 68$.

FIGS. 6 and 7.—Rat lung. Hæmatoxylin and eosin $\times 250$. Crystals in alveolar walls and spaces. The black masses are crystals out of focus.

FIG. 8.—Rat lung. Hæmatoxylin and eosin $\times 250$. Large hydropic cells in alveoli.

THE TOXICOLOGY OF ZIRCON: PRELIMINARY REPORT

BY

H. E. HARDING

From the Department of Pathology, Sheffield University

(RECEIVED FOR PUBLICATION, JANUARY 8, 1948)

Zircon, ZrSiO_4 , is found in alluvial deposits derived from igneous rocks mainly in New South Wales, Brazil, and South-West India (Jones, 1943). It is a very heavy, crystalline material with remarkable refractory properties and of very low solubility. The mineral is available in large amounts, and has been used for some time as a substitute for silica in the foundry industry as a parting powder and as a paint for moulds: its use as a substitute for sand in moulds has been advocated.

The distributors and the industrial users of zircon believe it to be entirely harmless, but there is no record in the literature of any assessment of its possible action in animals: indeed there are very few references to any of the compounds of zirconium. Kaestle (1909) advocated the use of the insoluble oxide of zirconium as a contrast medium for radiographing the alimentary tract: he considered that it should be harmless since it would not be absorbed. He injected a suspension containing several grammes intramuscularly into a rabbit, which showed no ill effects for eight months afterwards: there was no loss of body weight, and the urine was free from protein and casts: he described the material as "healing in" without reaction. Subcutaneous injections of a soluble salt into rabbits in doses of 0.4 g. per kg., were given without evident toxic results. Richet and others (1925) gave the soluble citrate in 1 g. doses for 146 days to four dogs whose weights appear to have been about 10 kg. The citrate was given by mouth daily, every other day, every third, and every fourth day, respectively. At the end of the experiment all the dogs appeared well, and none of them had shown any "accident" during the course. Their final weights were 110, 105, 112, and 109 per cent. of their initial weights. Van Nierkerk (1937) found that the soluble oxychloride had an inhibiting action on the contractions of isolated rabbit intestine, and lowered the blood pressure when injected intravenously into anaesthetized animals. He said that his findings confirmed those of Marui (1928), who used a complex salt with sodium tartrate which was toxic to mice and rabbits when injected in fairly large doses. Fairhall (1945) says that "zirconium has only a

mild pharmacological action and may even lack physiological effect in small amounts. . . . The zirconium compounds in chemical use are largely very insoluble, and no case of systemic poisoning has so far been reported."

Experimental

The zircon used in the experiments described here came from Travancore and had been ground to approximately 180 mesh. The analysis supplied by the distributors was zirconium oxide 62.23 per cent., ferric oxide 0.09, titanium oxide 0.10, rare earths not detected, phosphoric anhydride trace, combined silica (by difference) 32.58. It was a very heavy, light grey, powder that felt quite smooth when rubbed between the fingers, and that would remain suspended in a mixture of saline and skimmed milk for several minutes.

A full-grown rabbit was given four doses, each of 5 ml. of a sterile 10 per cent. suspension of zircon in physiological saline, intravenously over a period of seven days. The animal appeared in normal health thereafter until it was killed thirty-three weeks later. Nothing abnormal was seen at autopsy, and portions of several organs were fixed in formol-saline. Histological examination of the liver showed small clumps of faintly coloured crystals mainly close to the portal tracts: these clumps were within Kupfer cells which were distended to varying degrees (figs. 1-3). There was no trace of fibrosis or other reaction. There were small clumps of crystals in the splenic pulp: in the lungs crystals were present in small numbers in the alveolar walls, and some appeared free within the alveolar spaces (this is conceivably an artefact, the very hard crystals being dragged by the razor in cutting the sections). In neither of these organs was there any suggestion of a reaction to the presence of the crystals. No crystals were seen in the kidneys, which resembled the other organs in appearing histologically normal.

Approximately 3 ml. of a 10 per cent. sterile suspension in milk/saline was injected intraperitoneally into three cavies, which remained in perfect health until killed nearly a year later. Masses of

rather dry opaque material were embedded in the peritoneum of the abdominal wall and at points over the small intestine, and in the omentum. Sections showed large amounts of crystalline material enclosed in a cellular connective tissue in which were occasional giant cells having up to six nuclei. The amount of reaction was certainly no more, and may have been less than that around collections of pure carbon graphite or a fairly pure rouge (Fe_2O_3) injected in similar manner into other animals.

Six young rats were given an intratracheal injection of 1 ml. of a 10 per cent. sterile suspension while anaesthetized with ether: three were killed after seven months and three after nine months. The rats grew normally and appeared entirely healthy. The lungs were removed in the condition of normal inflation, fixed in formol-saline, and radiographed: portions of several lobes were taken for sections. The only difference between the lungs of the individual animals, or between those in the two groups, was in the quantity of crystalline material remaining in the organs: this variation is a defect inherent in the technique since different animals exhale very different quantities of injection immediately afterwards. One animal in each group had retained all or most of the injected zircon, and a description of one of these that had survived nine months gives a picture of what had happened in varying degree in all. The lungs had a slightly opaque white appearance when first removed but did not otherwise appear abnormal. There was difficulty in cutting really good microscopic sections since the crystalline mineral tended to tear the tissue: some of the free crystals also fell out of the sections. Crystals were found free in the alveoli, included within alveolar walls, and at lymph junctions within the lung (figs. 4 and 5). Some of the mineral was within phagocytic cells but much of it was still free. Where mineral was included within alveolar walls there tended to be some cellular increase and some enlargement of cells in these walls, but there were no foreign-body giant cells and no nodules (figs. 6 and 7). A few alveoli were filled or partly filled by large cells that had a small central pyknotic nucleus and a faintly staining hydropic cytoplasm in which were a few tiny granules of pigment (fig. 8). These cells, which appear to be swollen histiocytes, are not uncommon in the lungs of rats which contain dusts of many varied kinds: at least in some instances the cytoplasm contains lipoid stainable with Scharlach R or Sudan. Nowhere in the sections is there any evident fibrosis.

Discussion

It is desirable that as much information as possible

should be quickly obtained about any harmful effects of zircon, which is already in use in industry and which is likely to be employed much more extensively. Any ill effects it may have upon workmen in the foundry and other industries are unlikely to show themselves clearly until many years have passed, by which time the number of those exposed to its action will have grown to a considerable total. The results of animal experiments may not be strictly comparable with the risks in man, but they frequently give a useful indication of the degree of these risks. These preliminary experiments suggest that zircon is no more harmful than certain industrial dusts that are commonly considered as harmless or, at least, as harmless in moderate amounts. The tissue reactions found to injected suspensions of zircon are never more than, and usually less than, those to iron oxide or to crystalline graphite. These experiments involve exposure to the mineral for up to nine months.

Experiments in which the exposure to zircon more nearly resembles the conditions in industry than those reported here, are needed before one can be satisfied as to the risk. Such experiments, in which animals spend several hours each day for some months in an atmosphere containing a heavy cloud of fine particles of zircon, are in progress and will be reported later. This further report will deal also with the extraordinary x-ray pictures obtained of the lungs containing zircon. At the moment it is possible to say that these further experiments seem likely to confirm the inert character of the mineral.

Summary

No record has been found in the literature of the toxicology of zircon (ZrSiO_4), the use of which in industry as a substitute for silica is likely to increase.

Suspensions of finely ground Travancore zircon were made intravenously into a rabbit, intraperitoneally into cavies, and intratracheally into rats. In none of these animals was there any evident interference with health or growth. Histological examination of tissues obtained several months later suggests that zircon is a singularly inert substance.

I am indebted to Messrs. Colin Stewart, Ltd., Winsford, Cheshire, for the sample of zircon and for the chemical analysis. The photomicrographs were taken by Mr. A. W. Collins, F.I.M.L.T.

REFERENCES

- Fairhall, L. T. (1945). *Physiol. Rev.*, 25, 182.
- Jones, W. R. (1943). "Minerals in Industry." London. p. 141.
- Kaestle, C. (1909). *Münch. med. Wschr.*, 56, 2576.
- Lendle, L. (1934). Heffter, A., and Heubner, W.: "Handbuch der experimentelle Pharmakologie," 3, Pt. 3, 1557. Berlin.
- Marui, E. (1928). *Fol. pharmacol. Japon*, 8, 20. (Quoted from Lendle.)
- van Nierkerk, J. (1937). *Arch. exp. Path. Pharmacol.*, 184, 686.
- Richet, C., Gardner, and Goodbody. (1925). *C. R. Acad. Sci. Paris*, 181, 1105.