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PATHOLOGY OF VINYL CHLORIDE
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During the last years a syndrome characterized by alterations of the skeleton, teguments, nervous system and hepatic function^{1, 2, 3, 4, 5, 6} has been observed among the workmen associated with vinyl chloride polymerisation process. An experimental programme has been performed in order to evaluate the toxic effect of vinyl chloride on the animal organism, and in order to try to reproduce in rats the acroosteolytic lesions observed in man.

MATERIALS AND METHODS

Twenty-five Wistar male albino rats, of average weight 150 gr., were exposed to vapours of vinyl chloride 4 hours a day for 5 days a week during 12 months. The animals were kept in a plastic air-tight container through which there was a constant flow of air containing 2% in weight, equal to 30,000 p.p.m. of vinyl chloride. At the end of treatment the surviving animals were killed at twenty-day intervals, and the paws, brain, liver, kidneys and thyroid were examined histologically after fixation, inclusion and colouration by the ematoxylin-eosine. Van Gieson, PAS, Weighert, Bielschowsky-Gomori methods. Twenty five rats of the same breed were set aside as a control.

RESULTS

During the period of exposure the animals were slightly soporific, but the first few months of treatment were well tolerated and the rats showed no change in body growth or behaviour and no organic alteration visible macroscopically or by radiological means. After ten months some of the animals began to show a decrease in weight, in aggressiveness, in their reaction to external stimuli, and often a disturbed equilibrium. Thirteen animals died from cardio-respiratory complications. Two animals died from hemato-peritoneum. Most of the animals showed pathological involvement

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of the brain, liver, kidneys, and thyroid. Six rats showed histopathological alterations of the skeleton.

The small metatarsal bones showed an extensive periosteal proliferation of cartilage-like material apparently originating by metaplasia directly from the bone. All around the newly formed cartilage the cellular components were compressed and arranged tangentially to the cartilage itself, forming a perichondral layer. The isogenous cartilagenous groups were irregularly arranged and their nuclei were of varying size and often number per cell. The edges of the cartilage were irregular, showing digital extroflexions resulting from a varying growth potential. There was also evidence of chondroid metaplasia in areas of mature compact bone, in which the cartilaginous elements were grouped around a central nucleus of bone, as in typical osteochondromatous processes. In the small bones the chondroid metaplasia was often very extensive and the bones seemed to be impregnated with a mucoid substance which altered the characteristic disposition of the bone tissue obliterating the cement lines. The skin of the paws showed areas of hyperkeratosis superficial thickening of the epidermis, vacuolization and degeneration of the basal layer, disappearance of the cutaneous adnexa and modest accentuation of the papillar layer of the derma. An almost constant state of edema was observed in the epidermic zone. The connective tissue showed dissociation of the collagen bundles and a diminution and fragmentation of the elastic reticulum. The small arterial vessels showed signs of endothelial fibrosis with a thickening and dissociation of the elastic membrane, often accompanied by a partial hyaline degeneration and homogenization of the walls and proliferation of the endothelium. Some of the vessels appeared completely blocked by a proliferation of the connective tissue in a formation not unlike that of onion skin.

The small nerve bundles were often surrounded and invaded by fibrotic processes. A microscopic examination of the brain revealed diffuse degenerative lesions of the grey and white matter. The external granular layer was often reduced and in some areas this was true also the medium sized and giant cells. Numerous examples were found of hypercoloured, atrophic neurons with disappearance of the nucleoli and sometimes also of the nucleus itself. At the level of the white matter there were zones of intense, reactive gliosis consisting for the most part of cytoplasmic and fibrillar astrocytes, some of which were arranged in a concentric disposition around the blood vessels. There was evidence of neuronal phagokaryosis with satellitosis and the deposition of neuroglial elements around the altered nerve cells.

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There was modest proliferation of microglial elements, especially in areas of more intense gliosis and zones of intense spongiosis showing an accumulation of astrocyte-type elements with basophilic cytoplasm and abounding in gemistocytic and microglial elements similar in appearance to "scavenger" cells. The cerebellum showed signs of atrophy of the granular layer which was often represented only by a few isolated nuclei. The layer of Purkinje cells was in some places profoundly modified, the cells appearing to be undergoing intense degeneration and all the various stages of this process were observed, from the whole cell to the small homogeneous bodies with indistinct outlines which represent the most damaged form of the cell. Except for small and limited areas, the molecular layer seemed to be well preserved.

The liver was often of increased volume, sometimes subicteric in colour, with a smooth surface and somewhat more brittle consistency than normal. A histological examination showed in the majority of cases signs of diffused interstitial hepatitis with numerous hepatic cells in the grip of regressive processes varying from torbid degeneration of the cytoplasm to necrosis with marked cytoplasmic and nuclear polymorphism. Some of the hepatocytes showed giant or double nuclei. In these areas of cellular necrosis a corpuscular exudation was always present consisting of round cellular elements of the lymphocyte or plasmacellular type. There was evidence of an abnormal proliferation of the Kupffer's cells, which were often hypertrophic. The triangular spaces appeared to be increased by the infiltration of round and polynucleated cells and eosinophiles showing marked polymorphism. The portal capillaries, centrilobular veins and sinusoids were often blocked by numerous centrally-located areas of partial necrosis, often accompanied by a diffuse steatosis in the form of small drops with clearly-defined areas of acidophile necrosis and the formation of elements similar to the round acidophile bodies of viral hepatitis and the "Councilman" bodies of yellow fever. In certain cases evidence was found of an intense fibrosclerotic reaction alongside the degenerative processes.

The kidneys did not appear to be excessively altered by the prolonged treatment with vinyl chloride, although they showed signs of tubulonephrosis, sometimes accompanied by chronic interstitial nephritis.

The thyroid often showed a colloid goitre and a marked increase in parafollicular cells.

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The control animals showed no histopathological alterations of the skeleton or of the various organs.

CONCLUSIONS

This research confirms that the animals are sensitive to the toxic action of vinyl chloride. The lesions of the bone and connective tissue are similar to those noticed in experimental osteo-latyrism and to those described in a man affected with acroosteolysis of the hands (Marin). It should be pointed out that the roentgenological findings of skeleton in man rests on cartilaginous transformation of the bone tissue. Therefore according to recommendation made at XVI International Congress on Occupational Health of Tokyo (1969) I should like some precautions to be taken in the manufacturing plants polymerizing vinyl chloride, such as reduction of the threshold limit value of monomer, and substitution of manual cleaning of autoclaves by automatic devices.

SUMMARY

The results of this investigation show that animals exposed to vapours of vinyl chloride may show degeneration of the skeleton and connective tissue with histopathological pictures similar to those observed in human acroosteolysis of the hands. The bones in fact undergo processes of intense periostium growth and diffuse, chondroid metaplasia. The connective tissue is dissociated into collagen bundles with a reduced number of cells, the elastic reticulum is markedly reduced and fragmentary, the small vessels of the deep layers of the derma show hypertrophy of the walls with a diminution and sometimes obliteration of the lumen, the nerve endings are surrounded and infiltrated by fibrous tissue. Degenerative processes of the parenchyma were observed in the brain, in the liver and in the kidneys.

NOTE: Figures on available copy were not suitable for reproduction. They are as follows:

Fig. 1 -- Periosteal proliferation of metatarsal bone of a rat 16th months old, exposed to vinyl chloride vapours for 12 months

Fig. 2 -- Periosteal proliferation of metatarsal bone of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months

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Fig. 3 -- Periosteal proliferation of metatarsal bone of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months.

Fig. 4 -- Chondroid metaplasia in mature bone of metatarsus of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months

Fig. 5 -- Chondroid metaplasia in mature bone of metatarsus of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months

Fig. 6 -- Chondroid metaplasia in mature bone of metatarsus of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months

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CANCEROGENIC EFFECT OF VINYL CHLORIDE

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The demonstration of oncogenic activity of some chemical organic compounds employed for the preparation of "plastics" has been widely investigated and the limits and the effectiveness of their oncogenic power have been well defined. The present investigation demonstrates that it is possible to obtain for some experimental models a marked carcinogenic response to a monomeric precursor, i.e. vinyl chloride, of plastic polymers which follows a peculiar pattern for different tissues and organs of the rat.

Twenty-six Wistar (AR/IRE) male albino rats, of the average weight of 150 gr. were exposed to vapours of vinyl chloride 4 hours a day for 5 days a week during 12 months. The animals were kept in a plastic, air-tight container through which there was a constant flow of air containing 3% in weight equal to 30,000 p.p.m. of vinyl chloride. At the end of treatment the surviving animals were killed at twenty-day intervals and the most important tissues and organs were histologically examined by conventional methods. Twenty-five rats of the same strain were kept aside as a control. During the period of exposure the animals were slightly soporific, but the first few months of treatment were well tolerated and the rats showed no change in body growth or behavior and no organic alterations visible macroscopically or by radiological means. 65% of the animals developed tumors of the skin and 26% of these showed tumors of the respiratory tract exclusively localized in the lungs. Very few animals developed tumors in the bone and in this case the tumors were localized in the metaphysical region of the femurs, and it is worthy to mention that the femurs of both posterior limbs showed the carcinogenic transformation.

Tumors of the skin

The skin transformation which developed more frequently in the para-aural region, has been the epidermoid carcinoma, but we have seen also papillomas and rarely mucoepidermoid carcinomas.

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Tumors of the respiratory tract

Even if as far as the percentage is concerned these occur in a smaller number, their morphologic appearance is mainly of an adenocarcinoma; only in one rat it has been observed a tumor of the epidermoid type. Sometimes the tumor showed an early developmental stage and consisted predominantly of cubic or columnar cells arranged as regular or irregular tubular and papillary elements supported by poorly developed fibrous stroma.

Tumors of the bones

In the metaphysical region of the four limbs a large proliferation of cartilaginous tissue arises outwardly to the periosteum and seems to derive directly out of the osseous cortical by the growth of its cells. The cartilaginous growth is dishomogeneous as it is shown by the extension of finger-like prolongations into the boundary of neoformed tissue. Beside the chondroblastic, chondrocytic and angiomatous areas, manifestation of noticeable growth power, there are cartilaginous zones with regressive features, as fibrosis and hyalinosis.

The results reported above indicated that vinyl chloride is an effective carcinogenic agent for the rat. As for many carcinogenesis studies, where multiple tumors arise at different sites, in different tissues and organs, the data obtained need to be evaluated considering a more prompt positive response according to the ideal concentration of the carcinogenic. It is noteworthy to emphasize that the cutaneous system represents an impressive pattern of susceptibility to the vinyl chloride. Another point to be considered is that all the cutaneous tumors developed in the same site, i.e., the region including the area in which submaxillary and parotid gland are located.

No implications to human pathology can be extrapolated from the experimental model reported in this paper.

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