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SUMMARY

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GALLIERA HOSPITALS OF GENOA

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THE ONCOGENIC EFFECT OF POLYVINYLCHORIDE

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[The following paragraph is an exact quote of the English paragraph which appears in the text at this point.]

Oncogenic activity of polyvinylchloride. Within an interval of about 550 days after a mixed treatment by PVC per os and intraperitoneally, in two rats (among 30 animals so treated) appeared a subcutaneous fibrosarcoma, in one of them with a malignant lympho-reticular tumor of the lung. The AA believe that PVC has a slow oncogenic effect, with various evolutive phases.

Key words: vinyl choride, VC - Polyvinylchloride, PVC.

INTRODUCTION

The recent cautious allarm concerning the possible oncogenic effect of polyvinylchloride (PVC) — though at this moment the precise mechanism through which it occurs is still unknown — would seem to be reasonably justified by the results of our experiments on Wistar rats. They were treated once intraperitoneally and then fed for seven months with pure PVC powder. The development of a malignant neoplasm in two f the thirty experimental animals, though not very significant statistically, sh uld n t be ignored considering that in both cases we are speaking f fibrosarcoma, with almost perfectly

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identical characteristics. Also, in both cases the connection between the action of the supposed cancerogenic substance and the tumor appears to be clear, considering that said tumors developed subcutaneously, where residues of polyvinylchloride remained in the same point where peritoneal inoculations were performed. This was confirmed by macroscopic and histological examinations.

PVC is known with certainty to have a generically "pneumoconiocenic" effect, both in the spontaneous pathologies of workers who deal with the storage of the substance (Szende, B. and colleagues, 1970; Lilis, R. and coll., 1976; Arnaud, A. and coll., 1978) and in the experimental field (Frongia, N. and coll., 1972, 1974)

Its possible oncogenic effect was foreseen, more than once, by Oppenheimer, B.S. and coll. (especially in 1955) and by Roe, F.J.C. and coll. (1967) in the experimental field; but only in 1977 di Casterline, C.L. and colleagues discovered squamous-cell carcinoma of the oral mucosa in a 22 year-old non-smoker who for many years had had a habit of chewing PVC-based plastic material. Wainofer, H. and Zannagl, N. reported a case of plurifocal hemoangiosarcomatosis (in the area of the abdominal aorta, kidney, encephalon) from a relatively brief and intermittent exposure to PVC, and never to VC, after a latency of almost 15 years.

In research conducted at this Institute (Dessy, E. and coll., 1976; Costa, V. and Frongia, N., 1978) subcutaneous lesions of a granulomatous-tumoric type with rich vasa neoformations were found in rats inoculated subcutaneously with one dose of PVC powder. The same type of lesions were found in the abdominal cavity (around the periepipith, the perisplene and the epiploon) of the rats which were injected with vinyl polymer intraperitoneally. In both experiments there was considerable hyperplasia of the normal peri- and para-bronchial lympho-histiocytaric cumuli, at times so voluminous as to surround the bronchial structures like a sleeve and obstruct and cut them off in part, thus reducing the size of the cavity considerably.

PERSONAL OBSERVATIONS

The two animals were part, as was said, of a group of 30 rats which were treated with PVC at an age of about 30 days (initial weight was about 80 g) and for 7 months were given it in their feed following an inoculation of the same substance directly into the abdominal cavity. The dosage of the powder which was injected, suspended in physiological solution, was 1 gram. The powder administered orally (in water ad libitum) was about 200 mg daily. After the treatment ceased, the animals were kept alive for the longest time possible. They were given a standard diet and were caged like normal rats. A year and a half after the PVC inoculation, two rats were killed because they had subcutaneous tumefactions the size of large walnuts, not attached to the skin nor to deeper tissues, greyish-pink in color, duro-fibrous in consistency with evident areas of necrocytosis and both superficial and deeper decomposition. Here and there, at times periferically, at other times in the most central areas, grey-white striated foci were observed in which it was easy to locate residue from the PVC inoculations. In the first rat, these tumefactions were located in the lateral-inferior area of the thorax, in the second they were located in the lateral abdominal area.

An examination of the other organs and apparatus did not show macroscopically interesting alterations, except that in the second rat (whose lungs showed greyish nodosity which was well-delineated and of firm composition, especially in the peri- and para- ileum area in direct contact with the large

bronchi). Those nodosities, when cut, appear smooth and uniform, compact, and grey-pinkish in color.

For the histological studies, fragments of the subcutaneous neoplasms of both of the rats were removed from different points, fixed in 10 % formalin and enclosed in paraffin. Coloration: hematoxylin-eosin, Mallory's trichromic; Hotchkiss-McManus; argentic impregnation according to Bielschowsky-Maresch.

The presence of neoplastiform nodules, or so they appear, near the lungs of one of the two rats caused us to examine this organ histologically. Samples of the lungs of both rats were taken for this purpose.

The histological examination of the subcutaneous neoplasm showed that, in both cases, a typical fibrosarcoma was present, however, its proliferation is fast and irregular as evidenced by numerous and more or less anomolous mitotic behavior and also by the congregation of large cells, which are more or less polymorphic, and which at times have more than one nucleus (especially in the second rat). These cell's characteristics are very different from the typical fibroblastic-type elements of the over-all histologic picture (fig. 1, 2, 3, and 4). Thus it is clear that in the midst of this neoplastic tissue, both periferically and in the central parts of the tumoral mass, granulomatous groups of istial cells exist engaging in macrofagic activity (fig. 5 and 6) which, (supporting the macroscopic observation of gray-white striated foci on a gray-pink background of the newly formed tissue), testify to the subcutaneous persistence of PVC powder at the point of inoculation in the abdominal cavity. It would seem more than justified, then, to suppose that this polyvinyllic material could be the first cause of the appearance of subcutaneous fibrosarcoma both in the first and second rat, thus excluding the hypothesis that the malignant tumor appeared spontaneously (which is not common anyway according to Thomas, C. and colleagues, 1977).

CONSIDERATIONS AND CONCLUSIONS

We now return to the question of the oncogenic effects of PVC, even though in our research only 2 of the 30 treated rats developed a subcutaneous malignant neoplasm. It is important to remember that analogous results were arrived at by other researchers (Oppenheimer, B.S. and coll., 1952, 1953, 1955) by implanting PVC film underneath the skin of the rats, whereas the use of PVC in the form of alcoholate sponges did not produce convincing results. In repeating the same research, Dasler, W. and Milliser, T.V. (1963) emphasized that some technical steps play a vital role in the outcome of the experiments (beyond the factors of the rat's race and stock), some of which are sterilization in an autoclave instead of by boiling and the planting of the sponges in distilled water instead of physiological fluid. By using these methoas; the AA. had provoked the development of subcutaneous fibrosarcoma in a high percentage of male rats of Holtzman stock which had been implanted with PVC alcoholate sponge, but only 18 months after the implant.

This last factor seems particularly important in light of our research. If, as we believe we can say with a certain amount of tranquillity, the vinyllic polymer has a cancerogenous effect, it can be demonstrated only over long periods of time (as opposed to monomer which has a relatively rapid effect), whatever the activating mechanism may be (possibly through the liberation of VC, as Oster, G., 1975 asserts). That should not seem strange when we consider that an authentic cancerogen like 9.10-dimetil-1.2-benzoantracen would require 5 months to provoke the appearance of subcutaneous malignant neoplasm in a rat through a whole series of successive steps from the generic

flogistic process to the granulomatose process and to the tumor (Thomas, C. and coll., 1977).

If sufficient weight is given to the time element, it would not be rash to hypothesize that (keeping in mind the life-span of a rat in comparison to that of a man) as far as humans are concerned it would take years of exposure to the risk (they could also be called "doses") and years of latency before a malign tumor would be provoked by the vinylic polymer. With this in mind, it would perhaps be important to review from a years-after perspective those cases of so-called "pneumoconiosis" from PVC reported by Szende, B. and coll., (1970) Lilis, R. and coll. (1976), Arnaud, A. and coll. (1978), and restart the experiments of Frongia, N. and coll. (1972, 1974) on guinea pigs and rats kept for more or less long periods in a work environment (a polyvinyl powder sacking plant).

Before concluding, we would like to mention another factor observed in on of the two rats. One showed multiple nodosity at a point para- and peri-ilear to the tissue which had already been macroscopically identified as neoplastic tissue, an identification verified by the histological examination. It was, in fact, an active and lively proliferation of apparently lympho-reticular cells of a discreet volume, polygonal in form, with large nuclei (even double) and hyper-anisochromic with homogenic citoplasm and mostly polychromatic (fig. 7). At times these elements are elongated or even egg-shaped, but never fused. Collagenic and reticular fibre webs are always present, even if intermittent. These cells are found with others which are more lymphocytically typical, with more or less mature characteristics. Small epithelial glandular tubules are also present with a certain frequency (fig. 8). In other parenchymal areas one observes discrete hyperplasia of the lymphatic peri- and para-bronchial formations, which at times tend to cut off the cavity through invasion and replacing of the walls.

Excluding that this may be metastasis of the subcutaneous fibrosarcoma, since the characteristics of the elements seem totally different, we must advance the hypothesis that in the lungs of the second rat, there was a neoplastic deviation of the hyperplasia of the lympho-reticular structure already reported by Dessy, E. and coll. (1976) and by Costa, V. and Frongia, N. (1978) in experiments with PVC — the same being true of the cases discussed above. It is possible, in other words, that we have verified the hypothesis advanced by Dessy, E. (Thesis for specialization in oncology, 1978) of a tumoral transformation of the hyperplastic lympho-reticular process sustained by the vinylic polymer and which could have taken place over time, keeping in mind that the rat had been treated by two means of contemporaneous administration.

In conclusion, it seems to us that the study of these two cases of subcutaneous fibrosarcoma in rats treated with PVC powder, at a distance of a year and a half from the beginning of the experiment, demonstrates that the substance can have oncogenic effects. This was supported, above all, by the fact that in one of the two animals, there occurred a tumoral process of the lympho-reticular type, even in the lungs. Though we cannot advance realistic hypotheses on the intimate mechanisms of action, it we seem nonetheless clear that such activity is rather slow, and that it is only over long periods of time that the various necessary phases are passed through, among which are a granulomatose process and an interplastic type of process.

SUMMARY

Approximately one year and a half after having treated thirty rats with polyvinylchloride peritoneally and orally, two of them developed subcutaneous fibrosarcoma. In one of the animals a malignant lymphoreticular tumor of the lungs also developed. The AA. feel that PVC has a slow oncogenic effect which occurs only over long periods of time and through various evolutionary phases.

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