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Information Section

ARTICLES OF GENERAL INTEREST

VINYL CHLORIDE DISEASE—AN IMMUNE COMPLEX DISORDER?

A recent publication (Ward *et al. Br. med. J.* 1976, **1**, 936) suggests that vinyl chloride disease or, more strictly, the vinyl chloride syndrome may be the newest recruit to the ever-growing band of immune complex disorders.

An immune complex disorder is a form of tissue damage resulting from the building up of aggregates consisting of antigen and antibody. The aggregates form a lattice-type complex which, under certain conditions, precipitates out of the fluid phase and is deposited in the microvasculature, particularly at sites rich in capillary networks such as the skin and kidney. The deposited complexes fix a substance called complement, and this results in the production of a local inflammatory reaction. Complement exists in the serum as nine individual proteins which are biologically inert; on activation, the components bind to one another in a sequential fashion, during which process some of the single components become biologically active, acquiring properties that influence capillary permeability and the movement of inflammatory cells.

The activation of the complement sequence can certainly be brought about by antigen–antibody complexes, but aggregated immunoglobulin and certain chemical compounds can also start the process. It is important, therefore, when assessing the changes produced in this connexion by vinyl chloride, to remember that the demonstration of complement activation does not mean unequivocally that it is due to deposits of immune complexes.

The vinyl chloride syndrome, like the classic immune complex disorder systemic lupus erythematosus (SLE), consists of lesions in many organ systems. It is reasonable to postulate that there may be an underlying pathological process which could account for the different clinical manifestations and, by comparison with SLE, such a process could be a hypersensitivity response mediated by immune complexes.

Dr. Ward and her colleagues had the opportunity to examine 58 patients referred from a single vinyl chloride polymerization plant. The patients were divided by clinical criteria into four distinct groups. Group 1 consisted of nine patients with overt signs and symptoms of vinyl chloride disease (*Cited in F.C.T.* 1976, **14**, 347). Group 2 contained 19 patients described as "moderately disabled and multisymptomatic". Group 3 was the largest group, consisting of 25 patients with complaints reflecting a variety of symptoms but with very few clinical signs, while group 4 patients, five in all, were asymptomatic.

The immunological findings relevant to the claim that vinyl chloride disease is an immune complex disorder were the demonstration of mixed cryoglobulins, the reputed complement changes and the demonstration of IgG and C_3 in the small vessels of the skin and muscles. Cryoglobulins are precipitated when the serum of some patients is cooled to 4°C, and the precipitates can be collected by centrifugation, solubilized and subjected to immunoelectrophoresis to determine their content. Although cryoprecipitates are usually found in immune complex disorders, they are by no means pathognomonic because it is very difficult to show that the precipitates are composed of aggregates of antigen and antibody. The immunoelectrophoretic analysis carried out by Dr. Ward could give no information on the nature of a putative antigen.

Low serum levels of C_4 and C_3 and the *in vivo* conversion of C_3 indicate that complement is being activated. Immune complexes can consume complement, and changes of charge reflecting complement activation are often found in immune complex disorders but, again, they are not pathognomonic. It is important, when exogenous chemical substances are suspected antigens, to check that they are not anticomplementary in their own right.

The demonstration by direct immunofluorescence of IgG, C_4, C_3 and fibrinogen in the lumen of vessels is good evidence in favour of deposited immune complexes. Unfortunately, Dr. Ward did not publish photographs of the fluorescence, and as this particular procedure is difficult to interpret, good photographs would help to convince any sceptic.

The remaining immunological findings are not impressive and do not add much to the evidence incriminating immune complexes in the aetiology of vinyl chloride disease. What is impressive is the close correlation between the positive immunological findings and the clinical groupings, positive results being recorded in 88, 58, 8 and 0% in groups 1, 2, 3 and 4, respectively. The fact that there is such a close correlation clearly suggests that the clinical manifestations of the disease are either caused by immune complexes of some type or cause the formation of immune complexes; vinyl chloride could be the causative agent in either case. There is no evidence in Dr. Ward's paper, however, to show that vinyl chloride induces monomer-specific antibodies. The data could be explained by postulating that vinyl chloride acts biochemically to produce tissue damage, which secondarily leads to an auto-allergic response with immune complex formation between 'self-component' antigens and antibody. The distinction depends on whether vinyl chloride functions as an antigenic determinant, a point that may appear academic, since the net result is a disease brought about by immune-complex deposits, but is important if the mechanism of action is

to be understood. Furthermore an understanding of the processes leading to the formation of immune complexes could influence the clinical management of the disabled patients and the monitoring of individuals at risk.

Dr. Ward and her colleagues are to be congratulated on pointing towards a possible aetiology of this disturbing syndrome. Their results must obviously be confirmed, preferably by an independent group, but this could prove difficult in view of the geographical localization of the patients.

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ADDING TO THE HEXACHLOROPHENE PICTURE

When first introduced as a bacteriostatic agent in soap and cosmetics and as a therapeutic means of controlling the gram-positive populations of bacteria on normal human skin, hexachlorophene (HCP) was considered innocuous apart from its ability to induce allergic dermatitis or photosensitivity in a small proportion of the population. In 1971, however, the FDA published a study indicating that HCP could produce central nervous system degeneration when fed to rats over relatively short periods (*Cited in F.C.T.* 1972, **10**, 275), and demonstrations that HCP could be absorbed in significant amounts into the blood stream of infants bathed daily with a 3% formulation (*ibid* 1972, **10**, 114) raised the question of its safety for this use. Subsequent studies have been discussed from time to time in this Journal, and in this article we consider further aspects of HCP toxicity reported since our last review (*ibid* 1974, **12**, 563).

Absorption in man

Gillespie *et al.* (*J. Hyg., Camb.* 1974, **73**, 311) studied the data from a maternity hospital in which dusting powder containing 0·33% HCP was routinely applied to the umbilical stump and trunk of neonates. The HCP content of blood from mothers before delivery and from infants at birth and at the age of 8 days was measured. In all but one instance, in which HCP was assumed to have been derived from the use of HCP-containing toilet preparations before delivery, HCP was absent or barely detectable in maternal and umbilical cord blood. Concentrations of HCP in blood from 8-day-old infants ranged from zero to 0·166 μg/ml, with a mean of 0·066 μg/ml, and were thus well below those known to produce toxic effects in animals. Nevertheless, the authors suggest that HCP treatment should generally be confined to use in hospitals and under medical supervision during the first 7–10 days of life. It should be used with caution on low-birth-weight babies and not at all on infants with burnt or excoriated skin.

Absorption of HCP by adults after daily whole-body washings with a 3% HCP preparation containing a detergent was determined by Calesnick *et al.* (*Toxic. appl. Pharmac.* 1975, **32**, 204). In 50 adult volunteers, blood HCP was measured initially and after 3 weeks during which all known sources of HCP were avoided. Two detergent-based products, each containing 3% HCP, were then applied daily to the whole body surface excluding the scalp, as a 3-minute application of 30 ml (900 mg HCP) with enough water for adequate lathering. Blood samples were obtained at 7-day intervals for up to 4 weeks after the end of treatment or until the concentration of HCP had returned to its pre-trial value. Among the 43 subjects who completed over 6 weeks of the trial, the blood concentration of HCP exceeded 1·3 μg/ml in four, two using each preparation, during weeks 4 or 5. Pooled data showed a mean HCP peak during weeks 3–5 of 0·5–0·66 μg/ml, falling during weeks 6–8 to 0·33–0·51 μg/ml and returning to the pretreatment level of 0·009–0·012 μg/ml within 2–3 weeks of the cessation of applications. These findings suggested that the chronic blood concentration of more than 1 μg HCP/ml required to produce neurological damage in rats is higher than that likely to result from repeated whole-body washing of adults with 3% HCP detergent preparations.

In a further absorption study in adults (Bye *et al. Br. J. Derm.* 1975, **93**, 209), Ultralanum, an ointment containing corticosteroid with 1·4% HCP, was applied to six adults in quantities of 15–60 g/week for periods ranging from 2 weeks to 17 months. Plasma concentrations of 0·03–0·30 μg/ml were found, but there was no clinical evidence of toxicity. No correlation could be found between plasma-HCP levels and the total treatment periods.

The possibility that infants may ingest HCP in milk has also been investigated (West *et al. Bull. env. contam. & Toxicol. (U.S.)* 1975, **13**, 167). Six samples of human milk, collected before restrictions on the hospital use of HCP were enforced, contained HCP in concentrations of <2–9·5 ppb (b = 10^9), with a mean of 5·7 ppb. Five milk samples obtained after restrictions were in force showed no HCP in two, <2 ppb in two and 8·3 ppb in the fifth. It was concluded that these concentrations of HCP, in the low ppb range, probably did not constitute a hazard to infants, although it would be interesting to study nursing mothers who, for good medical reasons, continue to use HCP preparations topically.

Human poisoning

A tentative correlation between encephalopathy in infants and the hospital treatment of neonates with HCP emulsions has been attempted by Shuman *et al.* (*Pediatrics, Springfield* 1974, **54**, 689), who examined brain specimens from 248 children who died below the age of 5 years. In 17 children, vacuolar encephalopathy was seen and was related to a history