R&S 113084

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BIO-MEDICAL RESEARCH
DOCUMENT DESCRIPTION FORM

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Brief Summary

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of experiments was performed according to the following schedule: −24 hours intramuscular tranylcypromine (20 mg. per kg.); 0 hour intravenous tranylcypromine (10 mg. per kg.); 1 hour intravenous procyclidine (5 mg. per kg.); 4 hours intravenous tranylcypromine (10 mg. per kg.). The neuroleptics were injected at different times before the rectal temperature was recorded.

Intramuscular administration of α-flupenthixol (0·3 mg. per kg.), given at −1 hour, did not change the temperature course during the experiment; neither did α-flupenthixol decanoate in oil (10 mg. per kg.) given intramuscularly 3 days before. The following depot neuroleptics were given intramuscularly at −1 hour: α-flupenthixol decanoate (F.P.T.-D, 10 mg. per kg.), fluphenazine decanoate (F.P.Z.-D, 2·5 mg. per kg.), pipothiazine palmitate (P.P.Z.-P, 10 mg. per kg.), and fluspirilene (F.S.L., 2 mg. per kg.). F.P.T.-D did not influence the response to procyclidine, but there was a more striking rise in temperature after the last dose of tranylcypromine. Five out of six rabbits given neuroleptics and only one of the six controls had a temperature exceeding 40°C. In the F.P.Z.-D group one of six rabbits died shortly after the administration of procyclidine (40·7°C). Death may have been caused by a cardiovascular effect, since a preliminary experiment in this laboratory demonstrated that such a drug combination may produce dramatic tachycardia. Another animal died in hyperthermia (43·4°C) after tranylcypromine. In the P.P.Z.-P group fatal hyperthermia developed in two of six rabbits (42·9 and 43·7°C) in response to procyclidine. There was a slightly brisker and more pronounced response to the administration of procyclidine in rabbits treated with F.S.L. compared with the controls and after the last dose of tranylcypromine fatal hyperthermia (44·3–44·5°C) rapidly developed in all rabbits.

Thus, in a total of twenty-eight rabbits pretreated with two doses of tranylcypromine, administration of procyclidine resulted in a moderate hyperthermia (temperature not exceeding 41·4°C) in some animals. After injection of a further dose of tranylcypromine 3 hours after procyclidine, only cases of moderate hyperthermia were recorded, except in animals which had also been treated with a depot neuroleptic preparation on the day of recording. Severe hyperthermia either in response to the administration of procyclidine or to the last dose of tranylcypromine was recorded in some of these rabbits.

It is remarkable that F.P.T.-D injected 3 days before the experiment did not influence the temperature course, whereas injection of any of the depot preparations 1 hour before appeared to do so. In a period of a few hours, only minute amounts of active substance could have been released from the intramuscular depot, whereas an amount sufficient to establish neuroleptic effect would have been released after 3 days.[1-3]

Under certain conditions neuroleptics may possibly aggravate the interaction between antiparkinson drugs and M.A.O.I.s. The reason for this is unknown. However, all three types of drugs may affect dopaminergic neuron systems in the brain. Treatment with an M.A.O.I. increases the concentration of dopamine. In addition to the anticholinergic effect many antiparkinson drugs inhibit dopamine uptake,[4] leading to an increased amount of dopamine in the synaptic cleft. An interneuronal feedback mechanism due to postsynaptic receptor blockade by the neuroleptics is probably not operating, since a receptor blockade can be demonstrated pharmacologically only about 24 hours after injection of a depot neuroleptic.[1] Evidence indicating the existence of a feedback control mediated via presynaptic dopamine receptors, has been reported.[5-8] Minute amounts of the neuroleptics liberated from the depot during the first few hours may possibly block the presynaptic receptors, resulting in an increased formation of dopamine. Since dopaminergic agonists increase body-temperature in rabbits,[9] the hyperthermia recorded in the present experiments might be due to an exaggerated dopamine response.

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CHROMOSOMAL AND DOMINANT LETHAL EFFECTS OF VINYL CHLORIDE

SIR,—Vinyl-chloride monomer (V.C.M.) is carcinogenic to rats [1] and epidemiological evidence has demonstrated its carcinogenicity to man.[2] It is known that most carcinogens are mutagenic, and therefore evidence of mutagenic effects in man and animals has been sought. In relatively limited studies Funes-Cravioto et al.[10] and Ducatman et al.[11] have described chromosomal aberrations in man exposed to V.C.M. during the manufacture of polyvinyl chloride (P.V.C.). We have examined a larger number of workers and extended the observations to dominant lethal studies in mice exposed to V.C.M.

We have studied 80 workers, 56 of whom had been working in the manufacture of P.V.C., and were thus exposed to V.C.M.: the remainder were working in plants and laboratories where exposure to V.C.M. did not occur. The exposed group consisted of autoclave workers, maintenance workers, and workers associated with the manufacture of vinyl chloride. Blood samples were taken and lymphocyte cultures prepared using standard Difco kits (Difco Laboratories, Detroit, Michigan, U.S.A.). Lymphocytes were cultured for 48 or 72 hours. All slides were coded before scoring to ensure unbiased analyses, and 100 cells from each individual were analysed using the classification of Buckton and Pike.[12] Workers who had been exposed to X rays, prolonged drug treatment, or recent viral infections were excluded from the study.

CHROMOSOMAL ABERRATIONS IN VINYL-CHLORIDE-EXPOSED WORKERS AND CONTROLS NOT EXPOSED TO VINYL CHLORIDE

Exposure category	No.	% B cells	% Cu cells	% Cs cells
Exposed	56	6·30	1·45	0·38
Non-exposed ..	24	3·63	0·46	0·09

The results from 48 and 72 hour cultures were not significantly different and these data have been pooled. The results are given in the accompanying table where it can be seen that there is a significantly increased ($P < 0·05$) percentage of B, Cu, and Cs cells in the exposed workers. These results, which confirm those of the previous authors,[10,11] suggest that vinyl chloride has a detectable effect on chromosomal aberrations in man.

To check whether any genetic effects could be induced in the germ cells we carried out a dominant lethal study in

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mice. Fifteen male mice per treatment group were exposed to levels of 30 000, 10 000, and 3000 p.p.m. of V.C.M. for 6 hours a day on 5 consecutive days, and an examination for dominant lethal effects in two females mated with each male for 8 consecutive weeks was carried out. There was no significant increase in the number of early deaths per implantation compared with a control group exposed to air alone, indicating that V.C.M. does not produce dominant lethal mutations in mice even at these exceptionally high levels.

It appears, therefore, that the mutagenic effects of vinyl chloride, expressed as chromosomal aberrations in lymphocytes, do not occur in the germ cells. The reason for this could well be that active metabolites of vinyl chloride are responsible for the toxic effects and these do not reach the testis. The potential danger of mutagenic effects on the fetus via the sperm does not therefore seem to exist.

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THYROID-CELL-MEMBRANE ANTIBODIES

SIR,—Attention has been drawn [1-3] to an association between various types of thyroid disease and infection with *Yersinia enterocolitica* serotype 3. Lidman et al.[2] have also shown, using an indirect immunofluorescent technique, that a high percentage of the sera containing agglutinating antibodies to *Y. enterocolitica* serotype 3 have antibodies which react with the membrane region of thyrotoxic thyroid epithelial cells. Following heat inactivation of complement, smooth-muscle antibody (S.M.A.) positive sera can be shown

Unfixed section of thyrotoxic thyroid displayed by indirect immunoperoxidase technique.

Note the linear staining of epithelial cell membranes. ×440.

to produce identical staining of thyroid-cell membranes.[4,5] However, it is clear that this is a different antibody since not only can it be removed by absorption with pig stomach but also it appears to be inhibited by complement.[6]

We report here our studies on an antibody, found in sera sent to our laboratory for routine autoantibody studies, which produces an identical staining pattern to that observed by Biberfeld et al.[4] (see accompanying figure). The 46 sera investigated in this study were collected over a four-month period. Their selection was simply on the basis of the brightness of the thyroid-membrane fluorescence on initial screening. The indirect-immunofluorescence technique used was similar to that described by Beck.[6] To determine the immunoglobulin class of the antibodies, specific antisera to G, A, and M were obtained from Wellcome Reagents Ltd, and D and E from Behringwerke AG. As observed by Biberfeld et al.[4] some thyrotoxic thyroids used as substrates gave no staining of thyroid-cell membrane with positive sera and therefore, once a thyrotoxic thyroid was found suitable, it was used throughout the study. The mean age of the patients was 59·2 years (range 18–89); the 46 patients comprised 26 females and 20 males. The clinical diagnoses are shown in table I.

TABLE I

Clinical diagnosis	No. of patients
Thyroid disease:	
Thyrotoxicosis	12
Hypothyroidism	1
Unspecified	2
Other autoimmune diseases:	
Pernicious anæmia	6
Rheumatoid arthritis	1
Autoimmune hæmolytic anæmia	1
Chronic active hepatitis	2
Alopecia areata	1
Malignant disease	3
Vascular disease	4
Infectious diseases	2
Miscellaneous	11

TABLE II—ASSOCIATED AUTOANTIBODIES

Organ-specific		Non-organ-specific	
Thyroid microsomal	4*	Antinuclear	12
		Smooth muscle	11
Gastric parietal cell	18	Mitochondrial	1
		Reticulin	8

* True frequency of this antibody could not be determined since when there was bright cytoplasmic fluorescence due to microsomal antibody this obscured cell-membrane staining.

It is evident that some 52% of patients with this particular antibody have clinical autoimmune disease. The mean antibody titre was 1/64 (range 1/8–1/512). The immunoglobulin class of the thyroid-membrane antibodies was as follows: G-45, A-34, M-16, D-6, and E-28. The nature and frequency of associated autoantibodies are shown in table II.

Like Biberfeld et al.[4] we have observed that, following heat inactivation of complement, 32 out of 44 sera containing smooth-muscle antibody reacted with sectioned thyrotoxic cells to produce an identical staining pattern, but this antibody does not show as wide a spectrum of immunoglobulin class as that found in the other group and is mainly of the IgG class. Clearly, however, there is some overlap since 11 of the unheated sera which were positive for thyroid-cell-membrane antibody also contained S.M.A.

The association between *Y. enterocolitica* serotype 3 and thyroid-cell-membrane antibody [1-3] is of interest. Infection with this particular organism is common in Scandinavia, but this does not appear to be so in the United Kingdom.[7] Of 30 sera (10 positive for thyroid-cell-membrane antibody, 10 positive for smooth-muscle antibody, and 10 negative for all autoantibodies) screened for evidence of infection with this organism none was positive. However,

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