

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

Intramuscular administration of α -dupenthixol (0.3 mg. per kg.), given at -1 hour, did not change the temperature course during the experiment; neither did α -dupenthixol decanoate in oil (10 mg. per kg.) given intramuscularly 3 days before. The following depot neuroleptics were given intramuscularly at -1 hour: α -dupenthixol 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 fluspiridene (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 tranlycypromine. 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 tranlycypromine. 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 tranlycypromine 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 tranlycypromine, administration of procyclidine resulted in a moderate hyperthermia (temperature not exceeding 41.4°C) in some animals. After injection of a further dose of tranlycypromine 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 tranlycypromine 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.⁵⁻⁶ 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, the hyperthermia recorded in the present experiments might be due to an exaggerated dopamine response.

Department of Pharmacology and
Toxicology,
E. Lundbeck & Co.,
7-9 Omløves,
DK-2500 Copenhagen Valby,
Denmark.

V. PEDERSEN
I. MØLLER NIELSEN.

CHROMOSOMAL AND DOMINANT LETHAL EFFECTS OF VINYL CHLORIDE

SIR, Vinyl-chloride monomer (V.C.M.) is carcinogenic to rats¹ 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.³ and Ducatman et al.⁴ 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

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
Not-exposed	24	3.63	0.46	0.09

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.⁵ Workers who had been exposed to X rays, prolonged drug treatment, or recent viral infections were excluded from the study.

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,^{3,4} 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

1. Cassson, A., Kehr, W., Lindquist, M. J. *Pharmac. Paris*, 1974, 8, suppl. 1, 13.
2. Watters, J. E., Roth, R. H. *J. Pharmac. exp. Ther.* 1974, 191, 82.
3. Quast, R. M., Horita, A. *Science*, 1974, 183, 539.
4. Matsuura, C., Iwamura, G. *Environ. Res.* 1974, 7, 387.
5. Green, J., L. J. *Occup. Med.* 1974, 18, 150.
6. Funes-Cravioto, F., Lambert, B., Lindsten, J., Ehrenberg, L., Nizman, A. T., Osterman-Golkars, S. *Lancet*, 1975, i, 459.
7. Ducatman, A., Hirsztom, K., Selikoff, I. J. *Mutation Res.* 1975, 31, 43.
8. Buckton, K. E., Pike, M. C. *Int. J. Rad. Biol.* 1964, 8, 439.

1. Nymark, M., Franck, K. F., Pedersen, V., Boeck, V., Møller Nielsen, I. *Acta Pharmac. tox.* 1973, 33, 363.
2. Jørgensen, A., Fredricson Overø, K., Hansen, V. *ibid.* 1971, 28, 339.
3. Jørgensen, A., Gøtzsche, C. G. *Psychopharmacologia*, 1973, 27, 1.
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The additional cases became ill 12-59 days after the index case, strongly suggesting secondary spread of infection. However, 9 of 10 cases were associated with a single, shallow, open pit well. This well was heavily contaminated with coliform bacteria and faecal streptococci, but *S. typhi* could not be isolated despite several attempts. A strain of *S. typhi* with an identical resistance pattern was isolated from household water in a neighbouring house, but, owing to cross-contamination of the water vessel, the exact source of the bacteria could not be determined. There were no typhoid cases in this household.

Control measures have seemingly interrupted transmission at this focus, since there was no further illness 8 weeks after the last case-finding. Measures included chlorination of wells, carrier surveys, public-health-nurse visits for case-finding, home treatment and hospital referral, vaccination, and special sanitation instructions.

This outbreak of chloramphenicol-resistant typhoid may represent a primary occurrence in Java. Our experience leads us to believe that chloramphenicol-resistant typhoid fever has been rare or absent in Indonesia in the past. Hopefully, it will not develop into the problem now existing in Vietnam and Thailand.

U.S. Naval Research Unit No. 2,
Jakarta Detachment,
A.P.O. San Francisco 96356, U.S.A.

R.S. Fadmaswati,
Cilandak,
Indonesia.

Suku Dinas Kesehatan,
Jakarta Selatan,
Indonesia.

WARREN R. SANBORN
MURAD LESMANA
DAVID T. DENNIS.

RETNO TRENGGONOWATI
KADIRMAN
IRMA LITA.

SUYANT.

JOINT INFECTION BY PASTEURELLA MULTOCIDA

SIR,—We read with interest the letter by Griffin and Barber¹ in which they described a woman with rheumatoid arthritis and a pyarthrosis caused by *Pasteurella multocida* in a knee containing a prosthesis. We have also seen a woman with rheumatoid arthritis and *P. multocida* septic arthritis affecting a knee containing a prosthesis; she was cured with parenteral antibiotic and without removing the prosthesis.

A 55-year-old woman had an 18-year history of severe seropositive rheumatoid arthritis. She had been maintained on 7.5 mg of prednisone and 5.2 g of aspirin per day. Several years previously she had undergone surgery with the placement of bilateral knee prostheses. A 2-week history of painful swollen right knee prompted admission to hospital. She denied chills or fever. She had a pet dog which often licked her extremities, but had never bitten or scratched her. The right knee demonstrated synovitis and there were no scratches or abrasions on the extremities. Arthrocentesis revealed fluid containing 45 000 white blood-cells/mm³ and grew a pure culture of *P. multocida* (confirmed by the Pennsylvania State Laboratory and the Center for Disease Control in Atlanta, Georgia). A pharyngeal culture from the patient's dog also grew *P. multocida*. Intravenous penicillin therapy (10 megaunits/day) and frequent joint aspiration led to clinical improvement and eradication of the organism from the joint after 14 days. To date there has been no continuation of the infection and no evidence of loosening of the prosthesis.

Both Griffin and Barber's patient and our patient had long standing rheumatoid arthritis, were receiving corticosteroids, and had a prosthesis in the affected joint. The infections were eradicated without removing the prosthesis.

1. Griffin, A. J., Barber, H. M. *Lancet*, 1974, i, 1347.

Unlike most gram-negative rods, *P. multocida* has significant in-vitro sensitivity to penicillin, being sensitive to 0.19-0.39 µg/ml of penicillin.²

The excellent response to medical treatment of pyarthrosis in a joint containing a prosthesis conflicts with the widely held view that the prosthesis must be removed to eradicate the infection.³ Medical management alone may be adequate to effect a cure in septic arthritis in joints containing prostheses, especially if the organism is sensitive to easily obtainable antibiotic levels.

Of additional interest is the reported increased ownership of pets, especially dogs, by patients with rheumatoid arthritis compared with controls with other types of arthritis and other medical problems.⁴ *P. multocida* is often the predominant organism of the oropharynx of dogs, cats, and other animals.⁵

Rheumatology Section, Philadelphia
Veterans Administration Hospital,
Philadelphia, Pennsylvania 19104,
U.S.A.

KENNETH H. MAURER
PETER HASSELBACHER
H. RALPH SCHUMACHER.

INTRA-ARTICULAR METHOTREXATE

SIR,—The successful use of systemic methotrexate in resistant psoriasis prompted us to try intra-articular methotrexate in a patient with chronic psoriatic arthropathy. He was a man of 49 with persistent bilateral knee effusions which had resisted local and systemic steroid therapy. Two injections, a week apart, of 2.5 mg of methotrexate were made into each knee. 2 weeks from the first injection the effusions disappeared and have not returned after 10 months. No adverse effects were observed.

Because of the dramatic improvement, we have subsequently used intra-articular methotrexate in eleven other patients with persisting knee effusions: one with psoriatic arthropathy, eight with seropositive rheumatoid and two with seronegative rheumatoid arthritis. Only two (in the seropositive group) failed to show either complete resolution of inflammation or striking improvement; and none showed either local or general side-effects.

This treatment seems to be simple, safe (because of the very small dose used), and effective. We report these preliminary results in the hope that others may try intra-articular methotrexate and better define its scope and limitations in the therapy of resistant inflammatory arthropathy.

Royal Devon and Exeter Hospital,
(Wonsford),
Barrack Road,
Exeter EX2 5DW.

G. H. HALL
A. C. HEAD.

HYPERTHERMIA IN RABBITS CAUSED BY INTERACTION BETWEEN M.A.O.I.s, ANTIPARKINSON DRUGS, AND NEUROLEPTICS

SIR,—Interaction between monoamine-oxidase inhibitors (M.A.O.I.s) and tricyclic antidepressants or pethidine is well known. Experiments in our laboratories have shown a similar interaction (producing hyperthermia) between M.A.O.I.s (tranylcypromine and nialamide) and anticholinergic antiparkinson drugs (procyclidine and benzotropine) in rabbits.

To determine whether neuroleptics influence the interaction between M.A.O.I.s and antiparkinson drugs a series

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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.

I. F. H. PURCHASE
C. R. RICHARDSON
D. ANDERSON.

SER.—Attention has been drawn¹⁻³ 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



Note the linear staining of epithelial cell membranes. $\times 440$.

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 ob-

served by Biberfeld et al.¹ (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.² 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.,¹ 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 1.

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

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

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.

The association between *Y. enterocolitica* serotype 3 and thyroid-cell-membrane antibody¹⁻³ 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,

3. Beck, J. S. Association of Clinical Pathologists Broadsheet, 1974, no. 69.
4. Mayr, N. S. Personal communication.

of 3 sera, sent to us by Dr N. S. Mair, taken from patients with antibodies to *Y. enterocolitica* serotype 3, 2 were shown to react with thyroid-cell membrane. Since *Y. enterocolitica* infection is uncommon in the United Kingdom we decided to screen all thyroid-cell-membrane sera (46) and control sera (negative for all autoantibodies) for raised antibody titres, using a complement-fixation technique, against a variety of organisms: influenza A and B, Sendai, adenovirus, psittacosis, respiratory syncytial virus, cytomegalovirus, mumps S and V, *Mycoplasma pneumoniae*, and *Coxiella burnetii*. There was no significant difference in antibody titres between test and control sera. It would appear therefore that in this country, unlike continental Europe, there is a different triggering mechanism for the appearance in the serum of thyroid-cell-membrane antibody. As yet, the nature of this infection, if it is such, is unknown.

It remains to be proven whether this antibody is of pathogenic significance in thyroid disease. Certainly of 3 patients who died and who were known to have thyroid-cell-membrane antibody in their serum, none showed any evidence of thyroid abnormality. Finally, using an organ-culture technique, a total of 24 thyroid-cell-membrane-positive sera and controls (negative for all autoantibody tests) were studied for possible effects on the uptake of ^{131}I by hyperplastic thyroid explants, a minimum of six to eight cultures being employed in each test. ^{131}I uptakes after exposure to test or control serum were determined as previously described.⁸ No difference between test and control sera was demonstrable.

We are indebted to Dr N. S. Mair, Public Health Laboratory, Leicester, for screening our sera for antibodies against *Y. enterocolitica* and to the virus laboratory, Department of Bacteriology, Foresterhill, for carrying out the other serological tests.

C. H. W. HORNE
R. D. BRIGGS
A. G. NICOL
LILLIAN M. HOPKINS.
University Department of Pathology,
Foresterhill,
Aberdeen AB9 2ZD.

A NEONATAL AND INFANT PHLEBOTOMY TOURNIQUET

SIR,—I have been using a simple but extremely efficient tourniquet, made from easily available disposable items, which may be of interest to doctors dealing with neonates and infants. This consists of a roller clip from a McGaw paediatric giving set and a De Lee suction catheter. It is essential that these two items are used for best results.

The catheter is passed through the roller clip so that a loop is created at the "narrow" end of the roller clip.



In application the correct degree of tension is easily judged and the roller is then pushed home to maintain this. Other advantages of this tourniquet are that its size is ideal; it is released easily and can even be dismantled in situ, so as not to disturb drips; it does not pinch the infant's skin; a separate tourniquet can be made for each individual neonate or infant and hence help to reduce cross-infection; and of course it is extremely cheap and easily replaceable.

Radiodiagnostic Department,
Hammermith Hospital,
London W12 0HS.

C. METREWELL.

8. Harbitz, Th.S., Beck, J. S. *Br. J. exp. Path.* 1971, 52, 231.

COMPARISON OF PLASMA CARCINOEMBRYONIC ANTIGEN AND ALPHA-FETOPROTEIN IN VARIOUS TUMOURS

SIR,—Among the many tumour index substances measured in clinical practice, the oncofetal antigens, notably carcinoembryonic antigen (C.E.A.) and α -fetoprotein (A.F.P.), have received much attention. Although these substances were originally thought to be specific for carcinomas of the alimentary tract¹ and hepatocellular carcinomas² respectively, further studies have shown that both can be raised in the plasma in other conditions.³

We have examined, by radioimmunoassay, the plasma C.E.A. and A.F.P. levels of 172 patients. The series consisted of cases of bronchial and mammary carcinoma, of miscellaneous chronic liver disease (cirrhosis, ethanol abuse,

PLASMA C.E.A. AND A.F.P. LEVELS IN VARIOUS TUMOURS AND LIVER DISEASE

Condition	Plasma-C.E.A.		Plasma-A.F.P.		Total no. of patients
	Normal < 20 ng/ml	Elevated > 20 ng/ml	Normal < 15 ng/ml	Elevated > 15 ng/ml	
Colorectal carcinoma with hepatic metastases	2	5	7	0	7
Bronchial carcinoma	17	13	29	1	30
Mammary carcinoma	7	12	19	0	19
Miscellaneous tumours	23	23	45	1	46
Liver disease (non-malignant)	29	41	67	3	70

chronic hepatitis, obstructive jaundice), of colorectal carcinoma with hepatic secondaries, and cases with miscellaneous tumours including melanomas and lymphoreticular tumours, all having liver scans for suspected metastatic involvement. The results are shown in the accompanying table.

More than half of the tumour-bearing patients had elevated plasma-C.E.A. levels, whereas only a small minority of these same patients had plasma-A.F.P. levels outwith the normal range. There was only 1 case where the plasma-A.F.P. level (47 ng/ml) was elevated while the plasma-C.E.A. level (16 ng/ml) was in the normal range. This patient had Hodgkin's disease. Other examples of Hodgkin's disease had normal A.F.P. levels. In one other patient, with bronchial carcinoma, the plasma-A.F.P. level (92 ng/ml) was higher than the C.E.A. level (28 ng/ml). In all other cases, plasma-C.E.A. values were raised, with normal or raised A.F.P. values, or the levels of both oncofetal antigens were within normal limits. Recently McIntire et al.⁴ reported that 3% of colorectal-carcinoma patients have high plasma-A.F.P. levels; none of the present group show these changes.

The conclusion from these results is that in patients with non-testicular and non-primary hepatic tumours, measurement of plasma-C.E.A. is, by itself, a more reliable index of disease activity than measurement of plasma A.F.P.

K. M. GRIGOR
S. I. DETRE
D. J. R. LAURENCE
U. STEVENS
A. MUNRO NEVILLE.

Chester Beatty Research Institute,
Fulham Road,
London SW3 6JB.

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