

ERYTHROCYTES FROM CANCER PATIENTS AND FROM BLOOD DONORS: HAEMAGGLUTINATION WITH MONOCLONAL ANTIBODY

Diagnosis	No. of samples	Haemagglutination result			
		Intact erythrocytes		Desialated erythrocytes	
		GM+ mono-clonal Ab	GM	GM+ mono-clonal Ab	GM
Group I					
Leukaemia	25/25	+	-	+	-
Hodgkin's disease	4/4	+	-	+	-
Non-Hodgkin's lymphoma	2/2	-	-	+	-
Myeloma	1	+	-	+	-
Ewing's sarcoma	1	+	-	+	-
Wilms' tumour	1	-	-	+	-
Bronchus	3/3	+	-	+	-
Larynx	1	+	-	+	-
Lung	5/5	+	-	+	-
Ovary	1	+	-	+	-
Breast	5/5	+	-	+	-
Astrocytoma	1	+	-	+	-
Leukaemia*	1	-	-	+	-
Wilms' tumour*	1	-	-	+	-
Yolk sac carcinoma*	1	-	-	+	-
Ewing's sarcoma*	1	-	-	+	-
Hodgkin's disease*	1	-	-	+	-
Leukaemia, relapse	1	+	-	+	-
Group II					
Blood donors	2/50	+	-	+	-
	6/50	+/-	-	+	-
	42/50	-	-	+	-
Group III					
Random patients	4/32	+	-	+	-
	28/32	-	-	+	-

*Off treatment. GM = growth medium.

surface of their circulating erythrocytes. For these studies we first prepared a rat monoclonal antibody (an IgG) against desialated human erythrocytes. Antibody in the culture supernatant does not agglutinate normal erythrocytes but directly agglutinates desialated erythrocytes down to a titre of 1 in 100 (unpublished).⁹ Preincubation of the monoclonal antibody with purified T antigen (kindly donated by Prof. G. Springer) inhibits this agglutination. Blood samples obtained from 50 tumour patients (group I) and from 50 blood donors (group II) were then tested for haemagglutination with the monoclonal antibody (unpublished). All samples were maintained at pH 7.4 and 4°C under sterile conditions and were tested within 24 h of sampling.

The results (see table) indicate that the T antigen is exposed on the erythrocytes of patients bearing a number of tumours, including an astrocytoma in 1 case. In this group 3 of the 5 samples were negative—2 from patients with non-Hodgkin's lymphoma and the third from a patient 5 weeks before cessation of treatment for a Wilms' tumour. Of the 50 blood donor samples 2 were positive and 6 showed slight agglutination; the remaining 42 were negative for T.

Besides the patients in group I, 5 out of 5 patients who had completed therapy for cancer and were off treatment were found to be negative for T on their erythrocytes. 1 patient, who had a relapse after 3 years off treatment for acute lymphoblastic leukaemia, was positive.

A third group (group III) consisted of samples obtained from patients at random: here the samples were tested before checking individual diagnoses. 4 out of 32 were positive, of which 1 turned out to be a sample from a patient on treatment for cancer. The other 3 were a 93-year-old with a poor diet and lung collapse, a patient with poor vitamin intake and recurrent stomatitis, and a patient with alcoholic liver failure. The remaining 28 were negative and included patients with anaemia, pernicious anaemia, diabetes mellitus, colitis, splenomegaly, pancreatitis, liver abscess, and arthritis.

The exposure of T antigen on the surface of erythrocytes of cancer patients was detectable at diagnosis (i.e., before the start of, and

therefore unrelated to, chemotherapy). Control tests showed that:

(a) Treatment of erythrocytes from cancer patients or from normal individuals with irrelevant rat monoclonals did not cause haemagglutination.

(b) Those erythrocytes that did not agglutinate with "anti-T" monoclonal antibody subsequently agglutinated following desialation.

(c) Preincubation of the monoclonal antibody with purified T antigen abolished its ability to agglutinate intact erythrocytes from cancer patients.

(d) Those intact erythrocytes that could be agglutinated by the monoclonal antibody were not agglutinated by autologous plasma or by naturally occurring anti-T antibodies.

This last observation suggests that the epitope recognised by the monoclonal antibody is distinct from that which binds naturally occurring anti-T antibodies. Also, although the monoclonal antibody binds T antigen isolated from erythrocytes we have no direct evidence that it is binding to T on erythrocytes from cancer patients.

Studies are in progress to assess the value of this new monoclonal antibody in monitoring patients on treatment for leukaemia.

We thank the following from Addenbrooke's Hospital, Cambridge, and Cambridge University for their cooperation in obtaining blood samples: Dr N. D. Barnes, Dr V. Broadbent, Dr L. Brandt, and members of the paediatric oncology clinic; Dr J. K. H. Rees (department of haematological medicine); Dr D. G. Bratherton and Dr T. Wheeler (radiotherapeutic centre); and Dr T. Gibson (regional blood transfusion centre); and Mrs Rosamund Svensson for her assistance in raising the monoclonal antibody. This research was funded by the Cancer Research Campaign (J. M.) and by the Medical Research Council (S. M.).

Division of Virology,
Department of Pathology,
University of Cambridge,
Laboratory Block,
Addenbrooke's Hospital,
Cambridge CB2 2QQ

JO MILNER

Department of Surgery,
University of Cambridge,
Addenbrooke's Hospital

SU METCALFE

MESOTHELIOMA IN A BRAKE REPAIR WORKER

SIR,—Merewether's speculation in 1933¹ that asbestosis would manifest itself in industries, including the manufacture of asbestos brake linings, where it was then unknown, was soon realised. In the United States asbestosis was reported in a brake lining weaver in 1940² and the British Industrial Injuries Act of 1948 included asbestosis as a prescribed disease among "brake liners". Reports of lung cancer in asbestos-exposed workers closely followed those of fibrosis, but among "brake workers" such cases at first seemed to be confined to those who worked in friction product manufacture and fabrication. Subsequently there were occasional reports of lung cancer and mesothelioma among workers installing and repairing friction materials. However, asbestos-related cancer in brake repair workers has attracted little attention, in part because of the belief that fibre remained locked into the brake lining matrix or was much altered by heat generated by braking. Dust in brake drums was observed by light microscopy to be "asbestos-free". Furthermore, the capacity of chrysotile, the main form of asbestos used in brake linings, to cause mesothelioma may be less strong.

We describe here a diffuse pleural mesothelioma in a man whose sole exposure to asbestos was to the chrysotile form during brake maintenance and repair.

A 55-year-old man was admitted to hospital in October, 1980, with right-sided chest pain and soreness when he breathed deeply. Chest X-ray revealed a right-sided pleural effusion, and a cytological diagnosis of mesothelioma was confirmed by biopsy and examination of resected tumour. The patient died in September, 1981.

This man had for many years worked in used car, tyre, and car repair businesses. Since the age of 19 he had serviced automobiles, including the replacement of brake linings. He had no history of construction or shipyard work or any other occupational contact with asbestos and had never lived near an asbestos-fabricating plant.

1. Merewether ERA. A memorandum on asbestosis. *Tubercle* 1933; 18: 69-81, 109-18, 152-59.

2. Stone MJ. Clinical studies in asbestosis. *Am Rev Tuberculosis* 1940; 41: 12-21.

best predictor of
(i), and significant
nly one measure

riate or accurate
it, however, that
wing conclusions
il a gold standard
us with as many

ndation. The serum
al Perth Hospital
hard E. Davis.

NA J. STANLEY
HOLAS DE KLERK
RIE MARGETTS
ROL BOWER

5) Dr Phillips and
by Buss and me.
the folate content
rk sh... be done
accur... as this
take to be made.
as made in 1977,
ren defined. Free
omended daily
alth and Welfare²
age of the U.S.
e Department of
d daily intakes for
mendations were
[for folic acid] are
ded daily amount

define the daily
n, together with
assessment of the

J. A. SPRING

GLUTAMATES
PATIENTS

body which binds
ates erythrocytes

ent on human cell
ic surveillance by
T may become
f Springer and co-
uman malignant
mal cells.⁸ Our
mours may have
t 550 000⁹) on the

gnesium, copper, zinc,
hold supply. *Br J Nutr*

rd for Canada. Ottawa:

s, 8th ed. Washington,

by no 15. HMSO, 1979.
no 15 (2nd impression).

an blood, of substances
929; 6: 236.
group MN specificities.

Precursors of the blood
a. *Transfusion* 1979; 19:

The pathological diagnosis of asbestos-related diseases in people exposed to chrysotile fibre is complicated by the fact that asbestos bodies do not form readily. Furthermore, in patients with mesothelioma asbestosis may not always be present. As in this case, analytical electron microscopy may be essential. Chrysotile in a biological environment is degraded chemically and physically so that light microscopy is a poor guide to chrysotile exposure.

The health and safety problem of brake maintenance and repair work has been outlined by Morgan.¹⁶ In the United States there are about 1.7 million workers in the new and used car business, accessory stores, and service stations, and another 435 000 in repair shops and garages. The risk of malignant asbestos disease among these workers seems to be low¹⁷ but mortality data have yet to be thoroughly evaluated. With the large numbers at risk, more cases may be seen in the future.

This investigation was supported by a grant from the N.I.E.H.S., ES00928. We thank Dr John H. Evans, University of Tennessee, for the tissue samples.

Environmental Sciences Laboratory,
Mount Sinai School of Medicine,
New York, N.Y. 10029, U.S.A.
Canadian Tumour Reference Centre,
Ottawa Civic Hospital, Ottawa, Canada

A. M. LANGER

W. T. E. MCCAUGHEY

VENOUS ULCERATION IN HYPOGONADAL MEN

SIR,—Dr Howell and Dr Burton (Sept. 18, p. 630) suggest that venous stasis is related to hypogonadism. In trying to find an endocrine biochemical explanation for their findings they have underemphasised considerations of surgical pathology and powerful social factors.

The cause of venous ulceration is generally accepted to be incompetence of perforating veins, most commonly on the medial aspect of the ankle. Failure of the valves in these veins causes hypertension in the cutaneous venules and leads to ulceration.¹ Venous hypertension produces increased capillary leakage of fibrinogen and tissue deposition of fibrin, causing local hypoxia and ulceration.² There is no evidence that the blood in these veins is static or hypoxic, and the term stasis ulcer is outmoded.³

Incompetence of perforating veins normally follows deep vein thrombosis due to trauma such as that which occurs in women after childbirth and is, therefore, not necessarily related to androgen deficiency. The deep vein thrombosis resolves by recanalisation with damaged valves. The full hydrostatic pressure from the chest may, therefore, be transmitted to cutaneous venules; this effect will clearly be more severe in taller men.

Howell and Burton do not define hypogonadism, but testosterone assays by standard methods showed no evidence of reduced testicular androgen production, despite the fact that they were done on a selected subgroup of patients who were unmarried or infertile. The height and obesity of the patients cannot, therefore, be related to this. The infertility might be related to a reduced sperm count as happens in some generalised diseases (e.g., cystic fibrosis). Any metabolic abnormality causing a low sperm count might predispose to venous thrombosis or reduce fibrinolysis, but since sperm counts were not done this is only speculation, the two cases of Klinefelter's syndrome being clearly exceptional.

The men in the ulcer group were less likely to be married than were the controls—this, unlike fertility, cannot be directly related to sperm production. Howell and Burton discuss the fact that obesity might prevent men from marrying but ignore the possibility that this might also be true of men with venous ulceration or low socioeconomic class.

Department of Surgery,
St John's Hospital,
Chelmsford, Essex CM2 9BG

A. M. C. THOMAS

16. Morgan C. Trouble in the auto repair shop. *Job Safety Health* (OSHA, DOL) 1976 (Dec): 21-28.

17. Nicholson WH. Brake maintenance investigation of health hazards in brake lining repair and maintenance workers occupationally exposed to asbestos: Final report to N.I.O.S.H. (in press).

1. Dodd H, Cockett FB. The pathology and surgery of the veins of the lower limb, 2nd ed. London: Churchill Livingstone, 1978: 246-66.

2. Burnand KG, Clemenson G, Whimster I, Browne NL. Extra vascular fibrin deposition in response to venous hypertension. *Br J Surg* 1976; 63: 660.

3. Browne NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; ii: 243-45.

VITAMIN A AND PAGET'S DISEASE

SIR,—The recent resurgence of clinical interest in vitamin A has come about primarily as a result of improved methodology, such as high-pressure liquid chromatography (HPLC), which has permitted the rapid separation and analysis of retinoids in small volumes of blood and tissue extracts.¹ In turn this is increasing our understanding of vitamin A metabolism and of the role played by the retinoids in disease—for example, the possible relation between serum retinol and the risk of cancer,² the development of hypercalcaemia in renal failure,³ and the reduced fetal growth seen in immigrant Asians in Britain.⁴

The role of vitamin A in bone disease warrants closer examination. In vitamin A deficiency there is bulky overgrowth of bony tissue and failure of absorption of previously formed bone.⁵ Both increased osteoblastic activity and reduced osteoclastic activity have been implicated in these changes, which are reversed in hypervitaminosis A. Retinol is a membranolytic agent and in organ culture directly causes destruction and resorption of bone. It also stimulates the release of parathyroid hormone both in man in vivo and in isolated bovine parathyroid glands.⁶

While studying the response of patients with previously untreated Paget's disease to the injection of a single dose of calcitonin we noted that the plasma calcium usually fell while circulating parathyroid hormone (PTH) concentrations (measured by a radioimmunoassay directed mainly at the amino-terminal of the peptide) increased. However, the magnitude of these changes and the time of peak response varied considerably from patient to patient. In view of the above reported effects of vitamin A, we measured (by HPLC) plasma retinol on the basal plasma samples obtained from the patients to see whether vitamin A might be a factor in this variability.

So far sixteen patients have been studied. Four showed no response to calcitonin (i.e., plasma calcium and PTH values did not change). One patient showed a continuous increase in plasma PTH over the 24 h when samples were taken and was thought to have hyperparathyroidism. We excluded this patient from our calculations. The relations between the plasma retinol and changes in plasma calcium (ΔCa = maximum fall of calcium occurring at a time, $T_{min} Ca$, after injection) and PTH (ΔPTH = maximum rise of PTH occurring at a time $T_{max} PTH$, after injection) were as follows:

	Correlation (r)
ΔCa^*	0.519 (p<0.05)
ΔPTH^*	0.417 (p>0.1)
$T_{min} Ca$	-0.606 (p<0.05)
$T_{max} PTH$	-0.853 (p<0.001)

*Including the 4 non-responders.

$T_{max} PTH$ varied from 5 to 12 h in the eleven patients who responded to calcitonin (figure).

These results support the view that vitamin A has a role in bone metabolism and PTH release. Our interpretation would be that inasmuch as plasma retinol is a measure of vitamin A status and/or availability of vitamin A for metabolism, the reduced interaction of vitamin A with the parathyroid glands results in a delayed response in the release of PTH after the hypocalcaemia induced by calcitonin. This hypocalcaemic response to calcitonin is characteristic of patients with increased osteoclastic activity.⁷ Patients with a reduced availability of vitamin A may have less

1. De Ruyter MGM, De Leenheer AP. Simultaneous determination of retinol and retinyl esters in serum or plasma by reversed phase high performance liquid chromatography. *Clin Chem* 1978; 24: 1920-23.

2. Kark JD, Smith AH, Hames CG. Serum retinol and the inverse relationship between serum cholesterol and cancer. *Br Med J* 1982; 284: 152-54.

3. Farrington K, Miller P, Varghese Z, Baillod RA, Moorhead JF. Vitamin A toxicity and hypercalcaemia in chronic renal failure. *Br Med J* 1982; 282: 1999-2002.

4. Maxwell JD, Ang L, Brooke OG, Brown IRF. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *Br J Obstet Gynaecol* 1981; 88: 987-91.

5. Navia JM, Harris SS. Vitamin A influence on calcium metabolism and calcification. *Ann NY Acad Sci* 1980; 348: 45-56.

6. Chestow BS, Williams GA, Norris RM, Baker GR, Hargis GK. Vitamin A stimulation of parathyroid hormone: Interaction with calcium, hydrocortisone and vitamin E in bovine parathyroid tissues and effects of vitamin A in man. *Eur J Clin Invest* 1977; 7: 307-14.

7. Burckhardt PM, Singer FR, Potts JT. Parathyroid function in patients with Paget's disease treated with salmon calcitonin. *Clin Endocrinol* 1973; 2: 15-22.

burden.

insent) shows chrysotile structure.

brake failure free chrysotile for example, by the work of Seshan,⁸ and Rowson.⁹ rum dust^{10,11} and tend to be is submicroscopic chrysotile a more significant source of refuting, and refuting of opportunity, during brake with chrysotile fibre both in as a transformed state) and as res liberated by machining. of chrysotile to cause evidence from asbestos textile chrysotile,¹² from workers: miners and millers,¹⁴ and

J Air Pollut Control Assoc 1968; 18:

friction material. *Ann Occup Hyg* 1970;

during brake maintenance. *Ann Occup*

microscopy in the determination of the in environmental research application.

debris of brake linings. *Wear* 1978; 47:

Asbestos exposure during brake lining 110-28.

S, Selikoff IJ. Asbestos content of dust r. *Proc Roy Soc Med* 1977; 70: 32-37.

stos. *Lancet* 1978; i: 484-89.

and duration of employment among asbestos: Proceedings of Dresden 1968: 161-66.

ald JC. Epidemiology of a primary 1970; 28: 914-19.

er 1975; 32: 258-59.