mid-alcohol flushing (and indomethacin) as predictors of future development of vascular disease.

The loss of the differential association between chlorpropamide-alcohol flushing and macroangiopathy in diabetics diagnosed more than 15 years ago underlines the need for cautious interpretation. In table II of the paper by Drs Barnett and Pyke the patients without chlorpropamide-alcohol flushing of both age ranges are unusual in their greater liability to macroangiopathy with the shorter duration of diabetes; as so often, one wonders how patients entered a particular study and what a "total population" study would show, though realising how arduous this would be. The fixity of the chlorpropamide-alcohol flushing phenotype is an underlying assumption of the interpretation of Drs Barnett and Pyke, but its all-or-nothing character has already been questioned (by Jefferys *et al* at a recent meeting of the British Diabetic Association's medical and scientific section), while Köbberling has failed to confirm via cheek temperature measurement any increase of chlorpropamide-alcohol flushing-positivity among maturity-type onset diabetics compared to non-diabetics or even to juvenile-type onset patients.

Finally, what are the substantial reasons to postulate any "role of prostaglandins in the aetiology of both (vascular) types of complications?" from the observations that (1) maturity-onset diabetics with chlorpropamide-alcohol flushing and without angiopathy have the flush blocked by indomethacin; (2) indomethacin acts to inhibit a prostaglandin synthetase; (3) intravenous infusion of prostaglandin E is followed by facial flushing; and (4) absence of chlorpropamide-alcohol flushing is associated with increased risk of angiopathy? It is reminiscent of last year's involvement of endorphins³ in the aetiology of maturity-type onset diabetes.

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¹ Barnett AH, Spiliopoulos AJ, Pyke DA. *Lancet* 1980; ii:164-6.

² Köbberling J, Weber M. *Lancet* 1980; i:538-9.

³ Leslie RDG, Pyke DA, Stubbs WA. *Lancet* 1979; i:341-3.

Bladder cancer as a prescribed industrial disease

SIR,—The correction (16 August, p 523) to Dr F J Darby's letter (17 May, p 1229) on this topic, altering his statement that "Because the carcinogens responsible for causing urothelial tumour were withdrawn from industrial use in the early 1950s, the number of cases should show a decline over the next decade" (p 1230) to "by the mid-1960s . . ." makes the statement neither true nor any less misleading to clinicians and others who have to help certain sufferers from urothelial tumours (or their widows or widowers) to obtain such benefits as they may be entitled to under Prescribed Industrial Disease Regulations No 39.¹ In any case the correction is incomplete, for "over the next decade" must also be altered by adding some 15 years to this time because of the long latent period (averaging about 20 years) which is involved.

Perhaps it may help to restate the situation. Dr Darby's letter, which because of the address on it will be deemed to express the official view of the DHSS, was a comment on a paper by Sheena

Somerville and others entitled "Bladder cancer as a prescribed industrial disease: a guide for clinicians" (23 February, p 540), which gave help in defining under what circumstances a claim under PD 39 regulations might succeed. If it is to do so two criteria must be fulfilled—firstly, the disease must be of the right sort and, secondly, the patient must at some time after 4 July 1948 have been in insurable employment in a situation where the right chemicals were manufactured, used, or liberated, even if the employment consisted merely in maintaining or cleaning the plant used or laundering clothes used by workers in some such plants if this was done professionally in or for the plant concerned. It is not necessary, in relation to any particular case, that exposure reached or exceeded any particular level (see the appeal of G E Rushworth in 1979,² where a tribunal commissioner stated in judgment, "I agree with what was stated by a commissioner in decision R I 2/77 'that the presence of even very small quantities of a relevant substance is sufficient for the prescription of PD 39.'"). Nor is it necessary in any particular case to show that the disease was in fact causally related to the occupation in relation to which PD 39 benefit is claimed.

The "relevant substances" are set out in the regulations¹ in a form not easily understandable by those who are not chemists; but Dr Darby's phrase "the carcinogens responsible for causing urothelial tumour" will, in my opinion, inevitably be construed as being synonymous and coextensive with the PD 39 list; and because of the "authority" given to it by the letters DHSS clinicians will be tempted to ignore a patient's working history after "the mid-1960s" when considering whether to advise that PD 39 benefit should be sought.

In fact, far from a decline in the number of instances where such benefit should be sought—as opposed to any diminution of the total number of cases of occupational bladder cancer achieved by the growing control of the conditions of manufacture and use of the at present recognised carcinogenic aromatic amines since about 1950—an increase in patients entitled to benefit is to be expected. This is because it is not, on the whole, patients who have been employed in the larger manufacturing and using industries who stand in need of advice, for their employers and unions tend to take care of this, but because of new situations where exposure to the "relevant substances" occurred are coming to light as scientific knowledge increases. Unfortunately such knowledge takes a long time to reach clinicians (and apparently the DHSS) and so needy patients or their families do not get such recompense as they are in fact entitled to.

One such example is the discovery a few years ago that the induline and some nigrosine dyestuffs as manufactured in this country contained about 0.8% of 4-aminodiphenyl,³ a carcinogen at least as potent as 2-(β-naphthyl)amine in humans. Although this level of impurity just keeps it out of the "prohibited substances" class of the Carcinogenic Substances Regulations 1967⁴ it should be remembered that the 2-(β-naphthyl)amine impurity in the rubber antioxidant Nonox S, blamed as the main cause of the severe outbreak of occupational bladder cancer in the British rubber industry,⁵ was about 0.2%. Induline has uses in the dyeing industry; in the rubber and plastic industry; in making varnishes and stains; and in making typewriter ribbons, carbon paper, and inks—to quote but a few examples. How many sufferers have as yet been advised to make claims relating to the use of induline dyes or products made from them and containing some of the 4-aminodiphenyl?

If, as Dr Darby contends, the urothelial carcinogens had indeed been withdrawn by the mid-1960s, why was it necessary to pass the Carcinogenic Substances Regulations,⁴ which did not cover all the "relevant substances" listed in the PD 39 regulations (but which dealt with no other substances), and which prohibited only a few of them, in December 1967? Why, in January 1979, did the Health and Safety Commission⁶ find it necessary to send a warning letter to several British chemical suppliers pointing out the possible illegality of their offering for sale "certain substances specified as Prohibited Substances in Part II of the Regulations."¹

Could, and would, Dr Darby or some other official of the DHSS issue an authoritative list of where the "relevant substances" occur in industry or products, and of the dates, if any, when they were withdrawn? If not, clinicians and other advisers, as suggested in Sheena Somerville's paper, will still have to seek advice from sources other than the DHSS.

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¹ Department of Health and Social Security. *Prescribed industrial diseases leaflet (NI 2 1973): Disease No 39*. London: DHSS, 1973.

² Reith D. *Decisions of National Insurance Commissioner* (case No 172/1). CSI 24/79. Glasgow: 1979.

³ Parkes HG. *British Rubber Manufacturers' Association Health Research Unit Bulletin* 1977; No 20.

⁴ Carcinogenic Substances Regulations 1967: Statutory Instruments 1967, No 879. London: HMSO, 1967.

⁵ O'Connor Mr Justice. *Cassidy T and Wright C v Dunlop Rubber Co Ltd and ICI Ltd: Judgement*. London: High Court of Justice, Queen's Bench Division, 1971:25.

⁶ Health and Safety Commission. *Advice to local authorities*. LAAIC/C/3/1, appendix. London: HSE, 1979.

Sauna-induced acceleration in insulin absorption

SIR,—Dr H J Cüppers and others (26 July, p 307) have responded to my article (14 June, p 1411), in which I reported a significant rise in ¹²⁵I-insulin absorption (as measured externally by gamma counter) in diabetic patients after a Finnish sauna. In their study the authors injected healthy subjects subcutaneously with 10 U of Actrapid insulin prior to sauna (30 min at 85°C) and determined the levels of serum immunoreactive insulin following the injection. As compared with the control day, no increase in serum insulin levels was observed after the sauna. On the basis of their failure to see a rise in serum insulin levels after sauna and on previous findings in animals suggesting local degradation of insulin at the injection site,¹ Dr Cüppers and his colleagues criticise the method of external measurement of insulin disappearance from the injection site employed in my study.

If, however, one compares my results with their data more carefully, there is no discrepancy in the results: I also failed to see any significant rise in insulin absorption after the first 25 minutes of sauna. It was only after a repeat 25 minutes of sauna that insulin absorption in diabetic patients was significantly higher than on the control day at room temperature. More recently we have demonstrated that when ambient temperature was raised from 20° to 35°C diabetic patients demonstrated a 50-60% increase in insulin absorption over a four-hour period.² This rise in insulin absorption was accompanied by a 25% increment in skin temperature (p<0.05) and a 2.3-fold increase in skin blood flow (p<0.05). These observations, in conjunction with our results during the sauna, clearly demonstrate an enhanced insulin absorption in diabetic patients exposed to heat for 50-240 minutes.

Regarding the claim that the external measurement of insulin disappearance from the injection site "... is not suitable to assess the circulating levels of exogenous insulin following its subcutaneous injection," a variety of studies have demonstrated that (a) the radioactivity registered externally correlates with the amount of extractable insulin at the injection site³; (b) in human studies a correlation has been observed between the disappearance rate of ¹²⁵I-insulin from the injection site (as measured by external detection) and the change in blood glucose determined at rest⁴⁻⁵ or during exercise.⁶ Thus the available data indicate that the external measurement of the fall in radioactivity at the site of insulin injection reflects the disappearance rate of ¹²⁵I-labelled rapidly