Workshop Reports

Chlorpropamide-Alcohol Flushing and Diabetes

Report of an International Workshop, 13–14 June 1980, Washington, USA

M. Harris¹ and R. D. G. Leslie²

¹National Diabetes Data Group, National Institutes of Health, Bethesda, Maryland, USA, and ²King's College Hospital, London, UK

The phenomenon of facial flushing after drinking alcohol in diabetic patients taking chlorpropamide (chlorpropamide-alcohol flushing, CPAF) has been known since shortly after the introduction of chlorpropamide for the treatment of diabetes. It has recently been suggested that CPAF is a genetic marker for a type of insulin independent diabetes, that diabetics who exhibit the flush are less likely to develop the complications of diabetes, and that the flush may be mediated by neuropeptides, thus implicating such peptides in the aetiology of diabetes. Clearly, CPAF has important implications for research into the aetiology and pathogenesis of diabetes. Equally clear, however, is the need to standardize the methodology and to establish the prevalence of CPAF in populations, in order to define its epidemiological and physiological significance.

The workshop was held on 13 and 14 June 1980, in Washington, DC, USA chaired by Drs. David Pyke (King's College Hospital, London) and Maureen Harris (National Institutes of Health, Washington) and sponsored by the National Diabetes Data Group, the National Diabetes Information Clearinghouse (both of the National Institute of Arthritis, Metabolism and Digestive Diseases), and the International Diabetes Epidemiology Group. The participants included experts in the fields of epidemiology, genetics, pharmacology, neuroendocrinology and diabetes.

While there is little doubt that there is an important underlying genetic susceptibility to both major types of diabetes, the nature of the inheritance of Type 2 (insulin independent) diabetes remains uncertain. Is CPAF a genetic marker therefore for Type 2 diabetes? At the end of this workshop CPAF emerged unscathed as an inherited trait, but with its relationship to diabetes still unclear. In particular, this uncertainty arose because CPAF may not be an all-or-none phenomenon, and because some epidemiological studies have failed to confirm the relationship between CPAF and Type 2 diabetes. The observation that subjects with Type 2 diabetes and CPAF are relatively free from retinopathy and possibly also from large vessel disease requires further investigation.

Inheritance of Facial Flushing

Charles Darwin first noted that facial flushing was an inherited trait. Nearly a century passed before Dr. P. H. Wolff (Boston) suggested that another form of flushing, alcohol flushing, might also be inherited. Dr. Wolff reported that some 70%–80% of Mongoloids and American Cree Indians showed facial flushing with alcohol compared with less than 10% of Caucasoids. The flushing response is apparently strongly inherited, since it is common among both the

relatives of affected Caucasoids and the offspring of Caucasoid/Mongoloid hybrid parents. Dr. R. D. G. Leslie (London) reported that identical twins behave similarly for CPAF, that is, if one twin flushes so does his co-twin; while, if a twin does not flush, neither does the co-twin, regardless of whether the twins are concordant for diabetes. CPAF appears to be strongly inherited since roughly half the offspring of affected parents themselves show the reaction and in two families the flush has been traced through three generations. However, such a pattern of inheritance might be shown by a polygenic trait and Dr. Leslie believed that this form of inheritance was quite possible. CPAF can be blocked by the prostaglandin synthetase inhibitors, aspirin and indomethacin, and by the specific opiate antagonist naloxone but not all subjects with CPAF show this response. Thus there must be more than one mechanism (and therefore gene) involved in producing CPAF. This is an important point since a polygenic trait is unlikely to serve as a good genetic marker.

Mechanism of CPAF

Chlorpropamide alcohol flushing starts in the periorbital region, usually within 20 min of a drink of alcohol, and spreads across the face to involve the flush area. The flush seems to be almost specific to the interaction of chlorpropamide and alcohol since it occurs only exceptionally with other sulphonylureas. Unlike the disulphiram reaction, which is often associated with vomiting and hypotension, CPAF is not unpleasant. Dr. Leslie thought that the flush was probably part of a systemic effect due to the interaction of chlorpropamide and alcohol, since some people described breathlessness with the flush and several subjects developed asthma during the response. Asthma induced by chlorpropamide and alcohol can be partially blocked by disodium cromoglycate and in one subject the asthma was blocked by naloxone and induced by an enkephalin analogue.

The mechanism of CPAF remains uncertain. Although two groups of antagonists have been shown to block CPAF, prostaglandin synthetase inhibitors and opiate antagonists, not all susceptible subjects respond to these antagonists; among those with diabetic complications, very few do.

The cause of alcohol-induced flushing is also unclear. Altered metabolism of alcohol has been suggested but remains unproven. Dr. Wolff found anticholinergic agents have no effect on the reaction but the beta adrenergic blocking agent, propranolol, did appear to modulate the response. Other reports have suggested that a combination of H₁ and H₂ receptor blocking drugs could prevent

facial flushing due to alcohol. Patients afflicted with rosacea are also prone to alcohol flushing. This disease has two components, a vascular element characterised by erythema and telangiectasia, and an acneiform component with papules and nodules. Dr. J. Bernstein (Chicago) reported that H_1 antagonists do not inhibit facial flushing due to alcohol in acne rosacea while intravenous naloxone (0.8 mg) does. Thus, the evidence is that endogenous opiates can cause facial flushing but it remains to be determined whether this is a direct or an indirect effect. The difficulty in determining whether blockade of a physiological response is due to a direct or an indirect action of the antagonist was highlighted by Dr. H. S. Jacobs (London) who has found that naloxone blocked menopausal flushing. However, naloxone also blunts the pulsatile release of luteinising hormone and the question therefore arises whether naloxone is acting by a direct effect on the skin vessels or indirectly by blocking luteinising hormone release. This dilemma only serves to underline the considerable complexity involved in the vascular and neural mechanisms of flushing.

Such complexity was summarised by Dr. D. Rabin (Nashville) who discussed three diseases associated with facial flushing; namely foregut carcinoids, medullary tumour of the thyroid and mastocytosis. Dr. Rabin presented evidence that histamine may be involved in the pathogenesis of foregut carcinoid. However, in mastocytosis the situation is more complicated since both prostaglandin synthetase inhibitors and histamine blockers affect facial flushing. There also appears to be an abnormality of prostaglandin metabolism in medullary carcinoma of the thyroid since prostaglandin synthetase inhibitors block flushing induced by calcium and pentagastrin. Somatostatin blocks both calcitonin release due to calcium in medullary carcinoma of the thyroid and histamine release after pentagastrin infusion in subjects with carcinoid tumours. Thus, in these diseases there appears to be a complex web of interconnected neurotransmitters responsible for facial flushing.

Recording the Flush

It was generally agreed that observing a flush is the simplest and perhaps the best method of determining the response. However, observation is both subjective and unsuitable for recording facial flushing in dark-skinned races. More objective measurements of facial flushing utilize the increase in either facial temperature or ear lobe optical density. Wolff found a thermocouple applied to the cheek was more sensitive than one applied to the forehead and the results correlated well with optical densitometry. Optical density, recorded either by transillumination or reflectance, was favoured by Wolff but most people have been using cheek temperature measurements. It is important to obtain a stable basal temperature using this technique. Subjects whose basal temperature is $> 34.5^\circ\text{C}$ may show flushing with chlorpropamide and alcohol without a rise in temperature. Indeed, both Professor J. Köbberling (Göttingen) and the King's College Hospital group (Drs. Leslie, Pyke and Barnett) found a correlation between the temperature response and the basal temperature, the lower the initial temperature the greater the temperature response. Köbberling also found sufficient variation in the basal temperature to limit the reproducibility of temperature responses in determining flushing. The King's group relied on the subject's sensation of flushing for their epidemiological studies, but they agreed that this was not ideal as subjects may be unaware of flushing. Since one can flush without a rise in temperature and have a rise in temperature without visible flushing, the question arises as to what is a flush and how should it be recorded. While one can assume no flush has occurred if none is visible and there is no increase in skin temperature, for the sake of practicality Köbberling and others arbitrarily defined a temperature increase of 1°C or more as a flush. A small amount of alcohol (40 ml of sherry) is generally suf-

ficient to provoke CPAF in susceptible subjects, though the dose of chlorpropamide required to reproduce the reaction is less certain. Ideally, chlorpropamide should be given for several days in order to attain steady state levels but this is not always possible. In the only comparison reported of the single challenge test versus chronic treatment with chlorpropamide, Leslie found a single challenge test underestimated the frequency of CPAF by at least 8%. Köbberling also underlined the poor reproducibility of a single challenge test and reported many subjects who show flushing with alcohol alone. Thus, the problem of how best to identify subjects liable to CPAF remains.

Prevalence of CPAF

Leslie and Pyke had found that in insulin-independent diabetics, most of whom were on chlorpropamide treatment, CPAF was found more often (40%) than in Type 1 (insulin-dependent) diabetics or controls (10%). Most strikingly, 80% of Type 2 diabetics with a first degree family history of diabetes showed CPAF. Both controls and Type 1 diabetics had been tested with a single tablet challenge test while the majority (86%) of the Type 2 diabetics were taking chlorpropamide regularly. Using the single tablet challenge test, Professor K. G. M. M. Alberti (Newcastle) found that some 30% of Type 2 diabetics reported flushing with chlorpropamide and alcohol and Professor H. Keen (London) reported that in another group of Type 2 diabetics 28% showed CPAF. Köbberling, using a two tablet challenge test and a questionnaire, found about 23% of a group of Type 2 diabetics showed CPAF. In none of these studies did the prevalence of CPAF differ from that found in a group of Type 1 diabetics or non-diabetic controls also tested with a single tablet challenge test. Thus, using the single tablet challenge test, there was no evidence from these studies that CPAF is associated with Type 2 diabetes or that subjects with a strong family history of the disease are particularly prone to flushing.

The original appreciation of the possible significance of CPAF came from the observation that members of a family with Type 2 diabetes diagnosed at an early age, "Mason-type" diabetes, all showed the reaction. Dr. Pyke reported that 32 of 38 such diabetics showed this reaction. Professor S. Fajans (Ann Arbor, Michigan) found that among three pedigrees with three to four generations of "MODY" (maturity onset diabetes of youth) 11 of 19 diabetic patients, all on long-term chlorpropamide therapy, were CPAF positive. Köbberling found that four of seven patients with MODY showed CPAF, although in one family of seven such diabetics none was CPAF positive. Thus, the reaction seems to be common in patients with this type of diabetes, but the exact relationship is unclear. For the moment, we must defer judgement as regards whether CPAF serves as a genetic marker for this type of diabetes. Fajans pointed out that MODY is a heterogeneous disorder so, at best, CPAF could only serve as a marker for one type of MODY.

Genetic Factors in Diabetic Complications

It has been suggested that patients with MODY are relatively free from diabetic complications. However, Fajans presented evidence that patients with MODY can develop large and small vessel disease and some families appear to be more severely affected than others. Among the diabetic members of six MODY families with at least 15 years of diabetes, 18% had evidence of microangiopathy (10% with decreased vision or blindness) and 36% had macroangiopathy (15% with amputations and 18% with myocardial infarctions).

If genetic factors are important in determining retinopathy in Type 2 diabetics, then we might expect identical twins to have simi-

lar degrees of retinopathy. Leslie reported that this was the case; of 22 concordant Type 2 diabetic twin pairs with diabetes of at least 10 years duration, 21 pairs were in the same category for retinopathy when it was classified as nil, mild or severe. The situation was quite different for Type 1 diabetics, among whom a number of affected twins fell into a different category for retinopathy from their co-twins. If genetic factors are important in determining retinopathy, it would be interesting to see whether CPAF is related to this complication. Dr. A. H. Barnett (London) reported that, of 291 Type 2 diabetics, 191 were CPAF-positive and 100 CPAF-negative. Fifty-four percent of the CPAF-negative diabetics had retinopathy compared with 25% of CPAF-positive diabetics of similar age and duration of diabetes, while after 15 years of diabetes, 50% of the CPAF-negative diabetics had severe retinopathy compared with only 7% of CPAF-positive subjects. Surprisingly, CPAF was also associated with relative freedom from macrovascular complications; in a selected group of 220 age-matched Type 2 diabetics 41% of the CPAF-negative subjects had evidence of macrovascular disease compared with only 24% of CPAF-positive diabetics. This difference related to cardiovascular and peripheral vascular disease but not to hypertension or cerebrovascular disease. Barnett reported that, in a group of 21 selected Type 2 diabetics with macro- and microvascular complications, the skin temperature response to chlorpropamide and alcohol was unaffected by indomethacin, while, of 20 uncomplicated Type 2 diabetics with at least 10 years of diabetes, 13 showed marked attenuation of CPAF by indomethacin. Using the single tablet challenge test, Professor Keen also found that Type 2 diabetics, who were CPAF positive, were less susceptible to diabetic retinopathy than those who were CPAF negative.

Neurotransmitters and Glucose Homeostasis

Whether these postulated associations between facial flushing and diabetes are correct or not, they have prompted consideration of the role of prostaglandins and neuropeptides in the pathogenesis of diabetes. Particularly, they have led to a reassessment of the work of Claude Bernard more than a century ago. Pyke described how Bernard induced diabetes by placing a trocar in the brain stem of a rabbit and how this "piqure" diabetes led to the theory that diabetes was centrally mediated through excess hepatic glucose output. The theory gained favour until the work of Mering and Minkowski, who showed that diabetes was due to insulin deficiency, and Banting and Best, who demonstrated that correction of this deficiency resulted in the control of diabetes. Insulin deficiency is the hallmark of Type 1 diabetes but insulin levels can be normal or even high in Type 2 diabetes. Thus, although Claude Bernard was wrong about Type 1 diabetes, he may have been correct about Type 2 diabetes. Does the hyperglycaemia induced by neuropeptides resemble that seen in Type 2 diabetes? Dr. D. Porte (Seattle) said that somatostatin can prevent totally an insulin response to a glucose challenge while the insulin response to a beta adrenergic agonist is normal, a situation analogous to that seen in Type 2 diabetes. It is the response of the islet cells in Type 2 diabetes which is abnormal. Nutrients directly control islet cell function, and the autonomic nervous system controls the responsiveness of the islet cells to stimuli. Thus neurotransmitters could well be involved in the pathogenesis of this type of diabetes.

Neurotransmitters can influence carbohydrate metabolism both centrally and peripherally. The meeting went on to discuss the influence of opiate-like substances on glucose homeostasis. When morphine is administered intravenicularly in the cat, it causes marked hyperglycaemia. Adrenalectomy or denervation of the adrenals prevents this response. Morphine has no such effect in the anaesthetized animal unless naloxone, a specific opiate antagonist,

is also administered, whereupon hyperglycaemia results. Naloxone itself is without effect. Dr. W. A. Stubbs (London) reported that naloxone in very high doses could block the morphine-induced hyperglycaemia. Opiates also have a direct effect on the pancreas. Dr. E. Ipp (Chicago) presented evidence that an enkephalin analogue influences secretion of both insulin and glucagon from the pancreas of an anaesthetized dog in a dose-dependent manner; at low doses the analogue suppresses glucagon secretion but has no effect on insulin secretion, while at high doses it increases secretion of both hormones. These hormonal changes do not influence peripheral glucose levels unless the dog is rendered insulin-deficient by alloxan, when the increase in glucagon alone results in hyperglycaemia. These effects can be prevented by naloxone and it was concluded that peptides with opiate-like activity may be important in glucose homeostasis.

It seems likely that opiate agonists have a direct action on islet cells. Dr. I. Green (Brighton, Sussex) found that both morphine and met-enkephalin stimulated insulin secretion from islet cells in culture at low doses but inhibited secretion in high doses. Both these responses were blocked by naloxone. Dr. J. W. Ensink (Seattle), using an islet cell mono-layer culture, found that met- and leu-enkephalin inhibited and morphine stimulated insulin and glucagon secretion and that these actions could be blocked by naloxone. These discordant effects of enkephalin and morphine led to speculation that different receptors might be involved and Dr. C. Pert (Bethesda) recalled that there was evidence for at least two, possibly more, different opiate receptors. Dr. Green presented evidence, using a peri-fused islet cell system, that both morphine and met-enkephalin affect the first phase of insulin release. Many other candidate neurotransmitters can also influence insulin response to glucose, including serotonin, prostaglandin and adrenaline. The relationship of these neurotransmitters was described by Dr. P. Robertson (Seattle) who demonstrated that both prostaglandins and alpha adrenergic stimulation can inhibit acute insulin response to glucose. Inhibition of prostaglandin synthesis using sodium salicylate actually increases basal insulin levels and augments glucose-induced insulin responses in man. Indeed, sodium salicylate can partially restore glucose-induced insulin responses in Type 2 diabetics.

The meeting was left in no doubt that neurotransmitters play an important role in glucose homeostasis but it remains to be determined whether they are involved in the pathogenesis of Type 2 diabetes.

Those present included:

Professor George Alberti, Dr. Jose Barbosa, Dr. A. H. Barnett, Dr. Joel Bernstein, Dr. George Cahill, Miss Jean F. Curran, Dr. John W. Ensink, Professor Stefan Fajans, Dr. Irene Green, Dr. Maureen Harris, Dr. Eli Ipp, Dr. Howard S. Jacobs, Dr. Desmond Johnston, Dr. Ernest Johnson, Professor Harry Keen, Dr. Abbas E. Kitabche, Professor Johannes Köbberling, Dr. Keatha Krueger, Dr. David Leslie, Mrs. Lois F. Lipsett, Dr. Stewart Metz, Dr. M. Nagulesparan, Dr. Leon D. Ostrander, Dr. Candace Pert, Dr. Daniel Porte, Dr. David Pyke, Dr. David Rabin, Dr. Gerald M. Reaven, Dr. Lillian Recant, Dr. Paul Robertson, Dr. Jerome Rotter, Mrs. Carolyn Siebert, Dr. Reuben P. Siraganian, Dr. Michael Stern, Dr. W. A. Stubbs, Dr. Brian Suarez, Dr. Brian R. Tulloch, Dr. Kelly West, Dr. Jonathan K. Wilkin, Dr. Peter Wolff, Dr. Arthur Zeiner, and Miss Karen Leighty, Miss Linda Bilkey

Dr. Maureen Harris,
Westwood Building, Room 607,
National Institutes of Health,
Bethesda, MD 20205, USA