LETTER TO THE EDITOR

STRESS AS A DIABETOGENIC FACTOR

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Sir,

It was interesting to read the article by Sharma *et al.* (26) on urinary VMA levels following coffee and alcohol consumption and smoking. They have postulated that these social habits might precipitate some of the stress disorders in which persistent elevation of catecholamines has been considered to be of aetiological importance. Diabetes mellitus may be a disease of this category.

Diabetes mellitus has a multifactorial and somewhat obscure aetiology. One of the poorly reasoned causes is mental stress resulting from conflict, frustration, and other such accompaniments of life. The first frank manifestation of the disease occurs, not uncommonly, when a person is coping with a difficult life situation. Some subjects manifest emotional conflict years before the development of frank diabetes (28). Under stressful circumstances, the beta cells of the islets in the pancreas are likely to receive multiple stimuli for release of insulin as explained below :

1. During acute stress, the release of catecholamines from the adrenal medulla is enhanced (14). Catecholamines activate adenyl cyclase, leading to intracellular accumulation of 3', 5'-cyclic adenosine monophosphate (cAMP) which mediates their metabolic effects (24).

2. Under conditions of mental stress, acute or chronic, the consumption of coffee or tea is likely to be high in an attempt to cope with the stress better. The action of methylxantines (e.g. caffeine) present in tea or coffee, and that of catecholamines, is synergistic (27), partly because methylxanthines release catecholamines (22, 23).

Methylxanthines also inhibit the degradation of cAMP by inhibiting phosphodiesterase, resulting in further accumulation of cAMP (24).

The effect of methylxanthines is not only by a mechanism different from that employed by catecholamines, it is also likely to be much more potent because of the enzyme kinetics involved (21). Phosphodiesterase reaction is a first order reaction (i.e. the cAMP concentration is much less than the Km of the enzyme for cAMP) so that, as the cAMP concentration is increased by adenyl cyclase stimulation, phosphodiesterase activity is also concomitantly increased. In such a relationship, the modification of adenyl cyclase activity by adrenaline (and other appropriate physiological effectors) should result in only small changes in intracellular concentrations of cAMP; that this is the case has been shown experimentally (6, 24). In contrast, the inhibition of phosphodiesterase by non-physiological agents such as the methylxanthines, along with stimulation of adenyl cyclase, results in large changes in the concentration of cAMP (21).

3. Stress, particularly prolonged, produces increased output of adrenocorticotropic hormone (ACTH) leading to elevated levels of corticosteroids (25).

4. Emotional stress brings about a release of growth hormone (9), in children as well as adults (5).

5. The combined effects of catecholamines, glucocorticoids, growth hormone and methylxanthines lead to the following combination of stimuli for the release of insulin :

(i) Hyperglycaemia is known to be produced or induced by all the four agents named above (1, 4, 7, 9, 27). Hyperglycaemia stimulates insulin release as part of a homeostatic mechanism to regulate blood glucose (28).

(ii) Caffeine has been shown to stimulate the release of insulin from foetal pancreatic explants, presumably through its effect on cAMP concentration (15).

(iii) Rats fed caffeine at a level of 18 *mg/kg* develop oral tendencies, feel very hungry and eat up all the food that they are offered (10). To achieve this dose of caffeine, a man would have to take 10-15 cups of coffee, not an impossible amount in states of stress. The influence of caffeine on food intake might be mediated by catecholamines. Caffeine has been shown to release catecholamines in the brain (3), and catecholamines have been shown to have a marked influence on feeding behaviour (17, 18).

Whether caffeine produces a feeding response and related oral tendencies in man is difficult to establish but constant nibbling is not uncommon during stress. Such a feeding behaviour would impose an unusually frequent glucose load on the individual, and would consequently require an unusually frequent release of insulin. Thus behavioural effects of catecholamines may be acting synergistically with their metabolic effects to increase the glucose load presented to the pancreas.

(iv) cAMP also stimulates triglyceride lipase, leading to elevated levels of free fatty acids (FFA) (2). FFA levels are raised also by growth hormone, though cAMP has not been incriminated in the mediation of this effect (5). Hyperglycaemia and elevated FFA are a biochemical paradox : they create a situation of generous supply of two alternative fuels. Elevated FFA depress glucose utilization; normally, a useful mechanism which comes into play in case of diminished glucose supply (16, 20). But in this paradoxical situation, the mechanism would only help perpetuate hyperglycaemia, providing an additional stimulus for insulin release.

(v) Growth hormone has been shown to stimulate the synthesis as well as release of insulin in *in vitro* experiments (19).

Endocrine and behavioural responses to stressful situations can thus result in an orchestrated attack on the pancreas to release its insulin. Repeated onslaughts of this type may lead to exhaustion of beta cells of the pancreas, leading to diabetes mellitus through a process similar to that postulated for exhaustion diabetes due to excess growth hormone (11, 12, 28).

The susceptibility to the postulated mechanism, of which caffeine is an important actor, may differ, however. Mice with a hereditary form of obesity have been shown to be unduly sensitive to the effects of caffeine. Replacement of drinking water by coffee for one week in these mice causes a drastic and prolonged (two months or longer) elevation of blood glucose (13). In this connection, it is interesting that human diabetes is also commoner in the obese, and has a clear hereditary tendency (28).

The observation that serum insulin may not rise in response to stress-induced hyperglycaemia (9) does not necessarily contradict this hypothesis. The absence of peripheral manifestation does not exclude operation of the beta cells of the islets at a near-maximal level. The presence of a battery of 'diabetogenic' factors in the face of refractoriness of insulin release mechanisms is, in fact, likely to prolong and accentuate the pressure on beta cells of the islets to work harder.

The mechanism postulated here may be signifiacnt for some diabetics, and offers interesting possibilities of prevention. It has been summarised in Fig. 1.

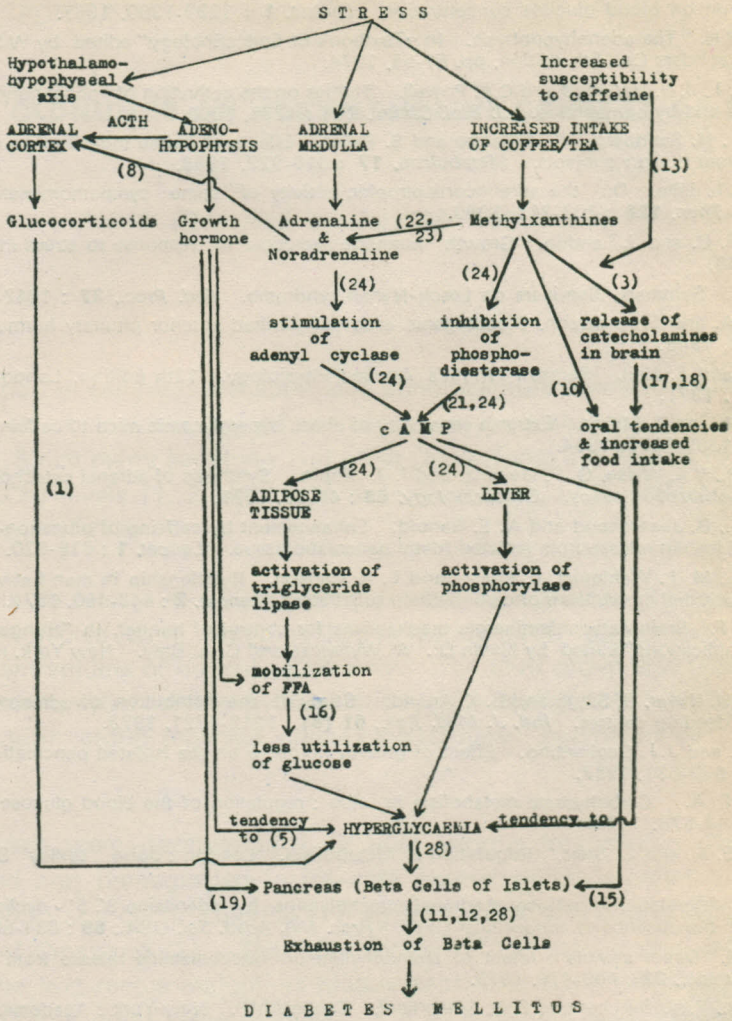

Fig. 1 : A hypothetical mechanism by which stress might lead to diabetes mellitus. Stress can possibly unleash an orchestrated attack on the beta cells of pancreatic islets.

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