COLD SWEATING, HYPOGLYCAEMIA, AND CARBOHYDRATE INSUFFICIENCY

WITH PARTICULAR REFERENCE TO COELIAC DISEASE

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That sweating is an exceedingly common phenomenon in ill children can be attested by any nurse or paediatrician. Much of this sweating is associated with pyrexia, but there are many disorders, particularly those of nutrition, in which a rise of temperature is not common and which have been classically linked with sweating e.g. rickets, prematurity, and pink disease. Cold sweating may be defined as sweating which occurs without an adequate thermal stimulus (Hemingway, 1944), thus excluding sweating due to cold stimuli (Kuno, 1934).

The possible clinical importance of cold sweating in children was suggested during investigations on insulin tolerance in children with coeliac disease. Nurses spontaneously remarked that the symptoms which were demonstrated to them as being due to insulin hypoglycaemia were of common occurrence in such patients and in other wasted ill children, occurring mostly during the night.

The relationship of cold sweating to hypoglycaemia is well recognized (Frostig, 1938; Himwich, et al., 1939). Himwich (1944) includes it in the first, and Wauchope (1933) in the second phase of progressive hypoglycaemia. By most it is assumed that the sweating is due to the adrenaline produced in the response to the hypoglycaemia (Cannon et al., 1924). Adrenaline usually does not produce sweating in man, sweat glands being cholinergic. In clinical association with cold sweating many other symptoms related to hypoglycaemia have been described e.g. colic (Quigley et al., 1929), and symptoms simulating appendicitis (Sandler, 1941; Brown, 1944). Further, the blood-sugar level at which symptoms of hypoglycaemia occur seems to be remarkably inconstant (Wauchope, 1933) even when allowance has been made for varying techniques and personal factors in observation.

Sweating is an easily recognized symptom and thus its relationship to the blood-sugar and carbohydrate metabolism is of some clinical importance. This paper records investigations of this relationship.

Clinical material. Three groups of children have been investigated: (a) seventeen normal convalescents; (b) thirteen children with coeliac disease, in which it has been shown that there is a state of carbohydrate insufficiency; and (c) three diabetics, who have a carbohydrate disorder. In each of these groups the relation of the cold sweating to the blood-sugar level has been observed in the hypoglycaemic period following the intravenous injection of insulin, and following the oral administration of glucose and intramuscular adrenaline. The relation of sweating to the intervals between meals was observed; the blood sugar estimated, and also the relative fasting sugar levels in the patients with coeliac disease and controls. The observations here reported have been confined to sweating for, although there were often other symptoms, sweating is by far the most constant early symptom of hypoglycaemia and the most easily noted; other changes such as pallor, dilatation of the pupil, and blood pressure changes, are difficult to assess and involve disturbing a sleeping child.

Technique. Details of the techniques used in the biochemical tests have been given in a previous paper (Emery, 1946), drug dosage being related to body weight (glucose 1 g. per kg., adrenaline 0.001 g. per kg., insulin 0.1 unit per kg.). The method of blood-sugar estimation used, that of Folin and Wu, records the reducing capacity of a protein-free filtrate of the blood, and the figures quoted in this paper have been corrected for true blood-sugar level (Herbert and Bourne, 1931). For convenience of record the degree of sweating was given arbitrary numerical values, the skin texture being estimated with a cool, dry hand:

- (0) skin of normal dry consistency;
- (1) skin moist in folds e.g. in palms or behind ears;
- (2) skin slightly moist all over;

FIG. 1.—Showing, in sample cases, the relationship of the blood-sugar level to cold sweating in time. Sweating is indicated by the thick blocked-in line at the base of the chart, the letters indicating to which curve each refers. Sweating is of category 2 (see text under technique) or over.

(3) roots of hair wet, particularly behind the ears;

(4) frank sweating, e.g. beads of sweat on brow, pillow damp, hair wet, etc.

Emphasis was laid on the head, as this is the only part of the body consistently available in the sleeping child without disturbing sleep. The numbers

given to the sweating categories are for convenience, and it is not suggested that category 4 indicates twice the sweating of category 2. In all cases when sweating is mentioned cold sweating is indicated, no child being used who during the test or for the two previous days had shown a rise in temperature or an increase in pulse rate.

Curve A = intravenous insulin tolerance test on a normal child.

Curve B = intravenous insulin test on a normal child in which adrenaline was given intramuscularly at the point marked by the arrow.

Curve C = intravenous insulin tolerance test on a child with the coeliac syndrome.

Curve D = intravenous insulin test on a child with the coeliac syndrome in which glucose (1 g./kg) was given at the point indicated by the arrow.

Curve E = intravenous insulin tolerance test on a child with the coeliac syndrome in which adrenaline was given intramuscularly at the point indicated by the arrow.

Curve F = intravenous insulin tolerance test on a diabetic child well controlled by insulin.

Curve G = a combined intramuscular adrenaline and oral glucose test on a coeliac patient who was cold sweating after fasting for four hours. The administration took place at 0 minutes.

Results

SWEATING FOLLOWING INTRAVENOUS INSULIN IN NORMAL CASES

Following the intravenous injection of insulin in eleven normal children, six showed abnormal signs, including sweating. The maximal fall in blood sugar occurred in all cases by twenty-five minutes after the injection, and was followed then by a fairly rapid return to normal. In all but one case the blood sugar was below 70 mg. per 100 c.cm. of blood (the generally accepted hypoglycaemic level) in ten minutes. The mean onset of sweating occurred at thirty-five minutes, in three cases there being no symptoms until after forty minutes. Thus there was a lag of between ten and twenty minutes between the blood sugar reaching a 'hypoglycaemic' level

and the onset of symptoms. Symptoms with sweating lasted ten to thirty-five minutes. This led to the situation that between fifty and sixty minutes after the injection, in all cases with sweating, the blood sugar had returned to within 30 mg. per 100 c.cm. of the resting level, and during the same time five of the six cases were still sweating (fig. 1, curve A). In one case (fig. 1, curve B) the onset of symptoms was exceptionally early, but the blood sugar had been below 60 mg. per 100 c.cm. for the eight minutes preceding the onset of symptoms. This child was then given an injection of adrenaline. The cases in which sweating occurred were not those showing the lowest levels of blood sugar; one case showing a fall of 65 mg. per 100 c.cm. from the resting level showed no symptoms.

It is thus demonstrated that cold sweating may

TABLE 1

GIVING THE RELATIONSHIP OF SWEATING TO INTERVALS BETWEEN MEALS IN SEVEN COELIACS AND SEVEN OTHER CHILDREN IN ADJACENT BEDS

The numbers refer to categories of skin texture described in the text under technique; (a) indicates awake and demanding food. The meals indicated consisted, in the coeliacs, of the usual fat low, high protein, diet and in the controls of normal hospital diet.

		TEA SUPPER MILK DRINK MILK DRINK BREAK-FAST DRINK DINNER																							
		Noon			p.m.			midnight							a.m.										
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
COELIACS	1	1	0	0	0	0	0	0	0	3	4a	3	3	4a	3	3	3	1	0	0	0	1	1	0	0a
	2	0	0	0	0	0	0	0	0	1	1	1	1	0	0	1	0	4a	1	0	0	0	0	0	0
	3	1	0	0	0	0	0	0	0	1	4a	1	1	1	1	0	1	0	4a	1	0	0	1	0	0
	4	2	2	1	1	1	1	1	1	4	4	4	4	4a	3	4	2	1	1	1	4a	2	4a	0	0
	5	1	1	0	0	0	0	1	1	0	0	0	3	3	1	1	2	1	0	0	0	1	0	1	0
	6	1	1	0	0	0	0	1	1	0	0	0	0	0	4a	0	0	0	0	0	2	0	1	1	0
	7	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	0	0	0	0	1	0	0	0
COELIAC TOTAL		6	4	1	1	1	1	3	3	8	13	9	12	13	14	9	13	4	9	3	3	7	5	6	0
CONTROLS	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0
	2	1	0	0	1	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
	4	1	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	
	5	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	
	6	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0
	7	0	0	0	0	0	0	0	0	1	1	1	1	1	1	2	1	0	1	0	0	1	0	0	0
CONTROL TOTAL		2	0	0	2	2	0	1	1	1	1	2	3	2	2	3	5	1	0	1	0	1	4	2	2

occur in normal children associated with insulin hypoglycaemia, there being a lag period of between ten and twenty minutes before the onset of symptoms after the blood sugar has fallen, which, in cases showing a normal rapid hypoglycaemic response, makes the symptoms coincide with the recovery phase or even follow it.

SWEATING FOLLOWING THE INTRAVENOUS INJECTION OF INSULIN IN DIABETICS

Insulin in standard dosage was injected repeatedly in two cases of juvenile diabetes, during experiments on the effect of fat intake upon insulin sensitivity in children. In no instance in these diabetics did sweating occur although the blood sugar fell rapidly, but the blood-sugar level was high (over 300 mg. per 100 c.cm. of blood), the depression produced by the insulin only bringing the sugar to normal levels.

A third diabetic, whose sugar level had been well controlled by insulin, produced sweating when the blood-sugar level fell to about 70 mg. per 100 c.cm. (fig. 1, curve F). It has been suggested that a rapid fall in blood sugar may of itself produce symptoms of hypoglycaemia, but symptoms were produced only in that case in which the blood sugar fell below 80 mg. per 100 c.cm.

It would seem that, in this very small group of diabetics, sweating is related to a low level of the blood sugar, and not to the actual falling of a high blood sugar or to the insulin itself.

SWEATING FOLLOWING INTRAVENOUS INSULIN IN CHILDREN WITH COELIAC DISEASE

Twenty intravenous insulin tolerance tests were performed on thirteen cases of the coeliac syndrome. In every case sweating occurred. The onset of sweating was earlier than in the normal controls and usually continued for at least thirty minutes, or until glucose, adrenaline, or some food had been given (fig. 1, curves C, D, and E).

The sweating and pallor, occurring in these cases with definite relationship to insulin and hypoglycaemia, was that which the nurses spontaneously remarked upon as being a common natural occurrence during the night. This observation was later confirmed by myself and resident house physicians.

THE EFFECT OF THE INTRAMUSCULAR INJECTION OF ADRENALINE ON SWEATING

In one normal case in which sweating occurred early following the injection of insulin, adrenaline was given intramuscularly, and sweating with other symptoms terminated within five minutes with a rapid hypoglycaemic response (fig. 1, curve B).

In two cases of coeliac disease adrenaline was administered following insulin at a time when previous control tests had shown that sweating and hypoglycaemia would continue for a long period. In both of these cases the sweating terminated in about ten minutes following the injection of adrenaline. In one, which was observed longer, sweating

was seen to reappear after a further period of twenty minutes. The blood sugar did not rise more than 8 mg. per 100 c.cm. and was still well below the usual symptom-producing level although the sweating ceased. In three cases when sweating was observed in patients with coeliac disease before the commencement of simple adrenaline tolerance tests, the sweating terminated within ten minutes of the injection of the adrenaline.

The only cases in which adrenaline in standard dosage was observed to produce sweating have been in children over the age of twelve who have at the same time felt frightened. In the coeliac cases the injection of adrenaline seemed to make them more happy and more lively than usual. The consistent findings in these cases were that adrenaline terminated the cold sweating, and this effect seems to be quite independent of the actual blood-sugar level.

THE EFFECT OF ORAL GLUCOSE UPON SWEATING

It has been shown that, following the administration of oral glucose in patients with coeliac disease after an injection of insulin, the blood-sugar returns to normal (Emery, 1946). The sweating invariably associated with the hypoglycaemia in these cases also terminated after a lag period of ten to fifteen minutes from the giving of the glucose. In all eight cases tested, the sweating had ceased before the blood sugar had returned to the resting level (fig. 1, curve D).

Two coeliac patients were observed to be sweating at the commencement of oral glucose tolerance tests. In these the sweating stopped within fifteen minutes of the administration of the glucose, although the blood sugar showed no appreciable rise at that time or subsequently.

Sweating terminated when intramuscular adrenaline and oral glucose were given simultaneously, in these circumstances associated with a great rise in blood-sugar level (fig. 1, curves D and G).

Thus oral glucose is able to terminate cold sweating, and this effect does not seem to be dependent upon the production of a rise in blood-sugar level.

COLD SWEATING RELATED TO INTERVALS BETWEEN MEALS

The skin texture of seven patients with coeliac disease and seven controls in adjacent beds were noted hourly over a period of twenty-four hours (table 1). The well-known clinical observation that coeliac children sweat more than others was confirmed. A definite relationship between meal-intervals and sweating was seen. From 6 a.m. to 6 p.m. meals were at three-hourly intervals, with occasional sweets as well, and a small amount of sweating was seen during this time. After 6 p.m. there occurred gaps of five and then six hours, and during this period there was a steady increase in the amount of sweating. This was most marked in the coeliac patients, but was also apparent in the others.

The milky drink given at 4.30 a.m. caused the sweating in the controls to return immediately to day levels, but the coeliac patients required a further meal at 6 a.m. before the sweating was much reduced.

Thus it would seem that in patients with coeliac disease there is a definite relationship between intervals between meals and cold sweating. Further confirmation of this was obtained later when Dr. Beryl Corner agreed to the institution in these cases of small frequent feeds two hourly, both day and night. A marked diminution in sweating occurred, and the general condition of the children also improved. Later, due to a misunderstanding, the night feeds were stopped and the excessive sweating recurred, to be diminished again by night feeds.

BLOOD-SUGAR LEVELS RELATED TO SPONTANEOUS SWEATING IN COELIACS

Samples of blood were taken from two patients with coeliac disease and two normal adjacent children at intervals during the night, and the degree

TABLE 2
GIVING THE BLOOD-SUGAR LEVELS AND SWEATING CATEGORIES OF TWO COELIAC AND TWO NON-COELIAC CHILDREN IN ADJACENT BEDS DURING A NIGHT FAST

		p.m.		a.m.							
		11	12	1	2	3	4	5	6	7	8
Coeliac (A)	Blood Sugar	68	—	—	68	—	56	—	69	—	69
	Sweating	1	—	—	3	—	4	—	0	—	0
Coeliac (B)	Blood Sugar	101	—	—	104	—	99	—	104	—	104
	Sweating	0	—	—	0	—	2	—	0	—	0
Non-Coeliac (A)	Blood Sugar	85	—	—	71	—	74	—	89	—	94
	Sweating	0	—	—	0	—	0	—	0	—	0
Non-Coeliac (B)	Blood Sugar	99	—	—	99	—	99	—	91	—	114
	Sweating	0	—	—	0	—	0	—	0	—	0

of sweating was noted (table 2). No food was given between 10 p.m. and 6 a.m. At 4 a.m. the coeliacs were sweating while the controls were not. The blood sugars of the coeliacs were 12 and 2 mg. per 100 c.cm. and the others 11 and 0 mg. per 100 c.cm. below the 11 p.m. levels. The greatest variation in blood sugar of the coeliac patients during the night was between 99 and 104 mg. per 100 c.cm., and that of the others between 74 and 85 mg. per 100 c.cm. After the 6 a.m. feed a rise in

blood sugar was more marked in the non-coeliacs. Two observations of interest seem to follow from these figures: (a) the sweating does not seem to be related to the actual level of the blood sugar. Coeliac B sweated with a blood sugar of 99 mg. per 100 c.cm., while control B did not sweat with a sugar level at the same time of 71 mg. per 100 c.cm.; (b) the amount of sweating does not seem to depend on a fall in blood sugar. (In coeliac A the 11 p.m. and 2 a.m. levels were the same, while sweating was much more profuse at 2 a.m. than at 11 p.m.)

FASTING SUGAR LEVELS IN COELIACS AND CONTROLS

The hundred and fifty-four estimations of the fasting sugar level were made during investigations on thirteen cases of the coeliac syndrome and eighty estimations under similar conditions in control patients. The mean level of the patients with coeliac disease was 93 mg. per 100 c.cm. of blood, and the controls 85.6 mg. per 100 c.cm. Fig. 2 shows the percentage frequency curves of these observations and it will be seen that the sugar levels in both groups have virtually the same range and distribution. It would thus seem that although in patients with coeliac disease there is a state of carbohydrate insufficiency this does not show itself by any lowering of the resting blood sugar.

Discussion

All recent publications have recognized that cold sweating is a symptom of hypoglycaemia (Himwich, 1944) and almost all observers within their own series remark upon the variation in different cases between symptoms and the actual sugar level (see Wauchop's review, 1933). In these investigations

FIG. 2.—Showing percentage distribution curves of the four-hour fasting sugar level in children with the coeliac syndrome (154 estimations) and in control convalescent children (80 estimations). A=coeliac. B=normal.

a similar relationship has been noted between hypoglycaemia and cold sweating in convalescent children, and cases of coeliac disease and diabetes. The most significant finding is, however, the lack of correlation between the actual level of the blood sugar and the cold sweating. This is seen in the sweating of fasting and in that produced by insulin. The most marked dissociation was seen when sweating was terminated by glucose and adrenaline following insulin. It is, nevertheless, probably correct to say that sweating can be induced in any child provided the blood sugar is lowered enough by insulin. Furthermore, while it is definite that children with coeliac disease are much more liable to cold sweats than other children, it is equally demonstrated that the blood-sugar level in the fasting state is at least as high as normal.

The question that immediately arises is whether the sweating produced by insulin is of the same etiology as that occurring spontaneously related to food. It is well recognized that in adults there are many causes of cold sweating (List and Peet, 1938) but little work seems to have been done on children. The sweating of hypoglycaemia and that of fasting both respond similarly to the administration of oral glucose and intramuscular adrenaline: and this of itself is enough to suggest a common background, probably of acute glucose deficiency.

That starvation does not produce a lowering of the blood sugar in children was shown by Ross and Josephs (1924) and it would have been surprising, if, in the long fasting periods when sweating occurred, the blood sugar had fallen to any great extent. It is most probable that the cold sweating to which coeliacs are abnormally liable is related to their lack of available glucose (or some closely related substance). The position seems to be that sweating is often related to the lowering of the blood sugar, but it is not dependent upon the sugar level, and is more dependent upon the state of carbohydrate metabolism which is liable to be associated with a fall of blood sugar. As oral glucose terminates this sweating, its cause could be an acute lack of available glucose products; and this theory would adequately explain all the observed reactions and does not entail a static symptom-producing level of the blood sugar. The work on pyruvic acid and lactic acid would seem to support this thesis, as there does not seem to be a direct positive relationship between these substances and the blood-sugar level (Gillman and Golberg, 1943).

Two further points arise from these experiments, one concerning the action of adrenaline, and the other the lag period before the onset of symptoms.

Adrenaline appears to terminate the cold sweating with or without raising the blood-sugar level, and the most simple explanation of this would be that it makes some form of carbohydrate available. But it is very difficult to be certain in the body as to what reaction is necessarily a primary response to adrenaline. Since Cannon's work on hypoglycaemia, in which he demonstrated an increased output of adrenaline in hypoglycaemia by its action on the denervated heart, it has been generally assumed that the early symptoms of hypoglycaemia are due to an increased output of adrenaline. That such an explanation was not the complete picture was early demonstrated by the inhibition by adrenaline of hunger and hypoglycaemia contraction of the stomach (Bulatao and Carlson, 1924), and it is possible that sweating is an allied reaction. Further investigations are needed in humans.

The lag period between the blood sugar reaching low levels and the onset of symptoms varied from ten to twenty-five minutes; and in cases showing normal hypoglycaemia responsiveness this may lead to confusion clinically. Blood taken during or immediately following symptoms, if the latter are of short duration, will often give no hint of the previous low level of the blood sugar (fig. 1, curve A). Thus, single estimations of the blood sugar may be misleading when hypoglycaemia is suspected, as are cerebrospinal fluid glucose levels in hypoglycaemic coma (Mayer-Gross and Walker, 1945). In this paper the term hypoglycaemia has referred to a lowering of a previously known resting sugar level, and not to any particular sugar level.

Conclusion

Cold sweating in patients with coeliac disease can be interpreted as being due to an acute carbohydrate insufficiency whatever the blood-sugar level. It does not necessarily follow that the same applies to cold sweating in any ill child, but the findings reported indicate that the observation of cold sweating in any child should suggest the possibility of carbohydrate insufficiency and merit the administration of glucose.

'His stomach is the kitchen where the meat
Is often but half sod, for want of heat.'

(From Gee's (1888) original description of the coeliac syndrome.)

Summary.

1. Cold sweating often follows the lowering of the blood sugar by insulin (after a lag period of ten to twenty minutes).

2. A similar cold sweating occurs spontaneously in patients with coeliac disease, particularly after fasting.

3. Cold sweating following insulin and occurring spontaneously is relieved by glucose and/or adrenaline.

4. Children with coeliac disease are particularly prone to cold sweating but their fasting blood-sugar levels are at least as high as normal.

5. Cold sweating is not dependent upon any actual level of the blood sugar.

6. It is suggested that cold sweating in children with coeliac disease, and also possibly in other ill children, may often be due to acute carbohydrate insufficiency independent of the blood sugar level.

7. It is suggested that ill children liable to cold sweating should be given frequent feeds day and night.

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