audience is necessary and the manifestations of the attack are mainly an emotional display without overbreathing, which can be stopped by the patient at will.

Treatment

While the emergency treatment of the isolated attack is entirely along physical lines—restriction of the overbreathing by an outsider or the injection of calcium intravenously—nevertheless the prevention of further attacks almost always calls for the psychological adjustment of the patient. Also following an explanation of the mechanism, some patients can be persuaded to arrest the attack in the early stages by a conscious control of respiration. Others, however, deny that they consciously overbreathe or can control their respiration when they become over-anxious. Especially in those who have difficulty in arresting the attacks once the premonitory symptoms of anxiety have occurred, benefit frequently results from investigating the causes of their emotional upset: discussion of their maladjustments and steps taken to alter disturbing factors in their environment often bring about a rapid cessation of the attacks. We failed to persuade a few patients who were deliberately inducing fits to give up this useful refuge from their difficulties.

The giving of calcium, alkalis, or acids by the mouth did not diminish the rapid spontaneous onset of the attack. But the biochemical approach to treatment merits further investigation and offers an interesting subject for future research.

Conclusion

Our study of the above cases has suggested that many hysterical fainting attacks and fits have hyperventilation as a central mechanism. A wide variation is possible in the clinical features of the hyperventilation attacks in different patients, but they appear to fall within one syndrome. The individual variations seem to depend on the severity of the hyperventilation, the degree of autonomic dysfunction, and constitutional tendencies, both metabolic and neurological. Many problems remain as yet unsolved concerning the mechanism of this type of attack, but it is an interesting example of the way physiological abnormalities play a part in the production of apparently hysterical symptoms.

Summary

1. Over twenty cases have been collected in which fainting attacks or fits with hyperventilation were a central feature.
2. The attacks were generally precipitated by emotional disturbance in patients who showed personality and constitutional features suggesting hysteria.
3. The varying features of the attack are described.
4. Diagnosis and treatment are briefly discussed.

Our thanks are due to Professor Edward Mapother for permission to publish these cases.

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INSULIN-TANNIC ACID-ZINC SUSPENSION IN TREATMENT OF DIABETES MELLITUS

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Much interest has been aroused during the last few years by the introduction into clinical practice of new preparations of insulin, such as protamine insulin ("insulin retard"), protamine insulin (with zinc) suspension, and zinc crystalline insulin. In use these preparations possess the characteristic features of delayed onset in action and prolongation of their maximum effect for several hours beyond that of ordinary insulin, phenomena which have been studied experimentally and clinically by previous workers (Bennett *et al.*, 1937). Suspensions of protamine insulin (with zinc) begin acting in nine to eleven hours, and achieve their maximum effect in fifteen to twenty hours. The value of these new insulins in the treatment of diabetes mellitus is now generally accepted, and has stimulated interest in the clinical potentialities of combinations of insulin with other organic substances and metallic salts. Among the substances studied in this connexion may be mentioned ferrous chloride, magnesium and other allied metals, lipoids, and—of special interest—tannic acid (Bischoff and Maxwell, 1935). The influence of tannic acid on the physiological action of insulin was first demonstrated by Bischoff (1936) during an investigation upon the precipitation of insulin by tannic acid. Insulin in combination with varying proportions of tannic acid, when injected parenterally into rabbits, produced delayed absorption of the insulin with a prolonged hypoglycaemic effect. Gray (1936) consequently gave to diabetic patients hypodermic injections of insulin-tannic acid mixtures (made immediately before use), and noted a delayed but prolonged action of insulin. He also observed that in certain patients erythema and subcutaneous swellings developed at the site of the injections. He did not, however, consider that the skin reactions were a significant drawback to the use of such mixtures. The action of the tannic acid-insulin in animals was further studied in this country by Bavin and Broom (1937), who confirmed the findings of Bischoff and further demonstrated that the properties of the mixtures were enhanced by the addition of zinc (*Lancet*, 1937, **2**, 390).

It is the purpose of this communication to report upon a clinical trial of the Bavin and Broom preparation, with reference to the changes produced in the blood-sugar levels and the local results of subcutaneous injections.

The Effect on Blood-sugar Levels

The blood-sugar levels of nine selected diabetic patients were examined during three periods, in which the patients received exactly the same diet, given at the same times, but with hypodermic injections of different types of insulin. The first test was carried out after injection of ordinary insulin. This was followed by observations after injections of protamine insulin-zinc. Finally the routine was repeated after a dose of insulin-tannic acid-zinc. The latter was a stable light-brown suspension containing the insulin, tannic acid, and zinc already mixed;

and was made up in rubber-capped bottles in sterile form, its strength being 40 units per c.cm. The stability of the mixture was such that its strength remained undiminished for several weeks at room temperature. The mixture consisted of insulin and tannic acid in the proportion of 1 to 2, with the addition of zinc, 1 gramme to 500 units of insulin.

The nine diabetic patients were stabilized on diet with twice-daily doses of ordinary insulin before the start of the investigation. The diets consisted of four meals a day, timed as follows: breakfast, 7.30 a.m.; dinner, 12.15 p.m.; tea, 4.30 p.m.; supper, 7.30 p.m.

Doses of the insulins were given as follows:

1st day of test: ordinary insulin at 7 a.m. and 4 p.m.

2nd day: protamine insulin-zinc at 7 a.m. only.

3rd day: no insulin at 7 a.m., but ordinary insulin at 4 p.m.

4th day: insulin-tannic acid-zinc at 7 a.m. only

5th day: no insulin at 7 a.m.; ordinary insulin at 4 p.m., and resumption of usual routine.

The dose of insulin-tannic acid-zinc was the same as the dose of protamine insulin-zinc.

Blood sugars were estimated by the Folin and Wu method, and were examined as follows:

1st day (ordinary insulin): hourly from 7 a.m. until 6 p.m.

2nd day (protamine insulin-zinc): hourly from 7 a.m. until 6 p.m.

3rd day: at 7 a.m. and 8 a.m. only.

4th day (insulin-tannic acid-zinc): hourly from 7 a.m. until 6 p.m.

5th day: at 7 a.m. and 8 a.m. only.

Case 9 was examined hourly on the second and fourth days from 7 a.m. until 9 p.m. The routine of the third, fourth, and fifth days was repeated in Case 8 on a second occasion, so as to obtain blood-sugar readings from 6 p.m. until 9 p.m.

On the third and fifth days no insulin was given at 7 a.m., so as to examine the action of the previous dose, twenty-four hours after its injection. The conditions of experiment for the second and fourth days were made the same by giving the injection of ordinary insulin at 4 p.m. on the previous day in both cases.

The results are set out in Table I. Those for Case 9 are illustrated graphically in the chart, which is character-

TABLE I

	Injection		Blood Sugar (mg. per 100 c.cm.)																	Diet
	Preparation used	Units (single)	Hours after Injection																	
			B ↓	D ↓				T ↓				S ↓				B ↓				
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	24	25				
Case 1 . . .	I	{ 40 35* 40	157	176	230	223	148	85	136	223	167	151*	204	223	—	—	—	200	—	2,109 Calories C 264 P 85 F 73
	P-I-Z		200	334	400	378	308	223	263	286	250	149	370	400	—	—	—	—	—	
	I-T-Z		40	185	308	333	278	200	185	227	243	192	166	294	322	—	—	—	—	
Case 2 . . .	I	{ 25 20* 28	193	167	150	139	111	123	170	185	161	173*	158	145	—	—	—	—	—	1,060 Calories C 107 P 56 F 46
	P-I-Z		187	250	274	188	159	117	109	100	98	119	200	100	—	—	—	—	—	
	I-T-Z		28	—	100	244	196	182	—	166	166	133	139	148	159	—	—	—	—	
Case 3 . . .	I	{ 30 20* 30	286	351	267	182	110	61	119	136	143	147*	193	143	—	—	—	384	—	1,329 Calories C 154 P 60 F 55
	P-I-Z		384	416	435	425	344	314	324	—	267	286	334	400	—	—	—	91	—	
	I-T-Z		30	91	260	267	210	172	122	210	206	200	197	270	333	—	—	—	154	
Case 4 . . .	I	{ 20 20* 20	286	324	290	178	131	100	108	155	178	232*	267	196	—	—	—	278	—	1,981 Calories C 63½ P 100 F 148½
	P-I-Z		278	344	358	344	290	238	215	—	196	178	236	278	—	—	—	80	—	
	I-T-Z		20	80	161	244	208	162	119	109	105	75	70	200	195	—	—	—	366	
Case 5 . . .	I	{ 15 12* 16	95	134	143	90	56	60	134	146	135	106*	91	120	—	—	—	106	—	1,329 Calories C 154 P 60 F 55
	P-I-Z		166	164	162	133	125	130	126	96	93	86	125	149	—	—	—	70	—	
	I-T-Z		16	70	84	133	62	57	60	120	87	95	95	202	250	—	—	—	—	
Case 6 . . .	I	{ 50 45* 50	133	125	123	—	75	62	80	86	100	90*	91	105	—	—	—	122	—	1,329 Calories C 154 P 60 F 55
	P-I-Z		122	166	270	264	222	238	204	244	208	190	213	208	—	—	—	185	215	
	I-T-Z		50	217	250	270	238	250	227	200	174	168	143	126	169	—	—	—	124	
Case 7 . . .	I	{ 20 10* 20	116	103	46	45	75	80	200	170	161	144*	230	235	—	—	—	166	—	1,329 Calories C 154 P 60 F 55
	P-I-Z		166	212	294	182	123	72	137	135	124	122	250	260	—	—	—	166	334	
	I-T-Z		20	100	233	263	222	143	106	162	125	113	93	166	267	—	—	—	125	
Case 8 : (October, 1937)	I	{ 20 10* 20	286	313	313	—	228	156	147	164	182	185*	238	257	—	—	—	286	—	1,329 Calories C 154 P 60 F 55
	P-I-Z		286	313	400	313	236	250	250	323	340	308	300	400	—	—	—	250	313	
	I-T-Z		20	328	400	408	364	303	282	290	313	244	244	274	313	—	—	—	303	
(November, 1937)	P-I-Z	20	274	—	—	—	—	—	—	—	—	—	274	317	286	270	317	256	318	854 Calories C 112 P 55 F 26
	I-T-Z	20	312	—	—	—	—	—	—	—	—	—	143	215	215	213	232	263	333	
	I	{ 30 25* 40	143	180	253	206	166	133	200	267	267	282*	308	240	—	—	—	182	—	
P-I-Z	182		267	364	285	244	247	250	299	263	294	351	303	260	223	238	157	208		
I-T-Z	40		137	244	295	250	233	238	266	286	250	238	270	263	217	194	270	150	240	

* Second injection of ordinary insulin.

I = Ordinary Insulin
P-I-Z = Protamine Insulin-Zinc
I-T-Z = Insulin-Tannic Acid-Zinc

B = Breakfast
D = Dinner
T = Tea
S = Supper

C = Carbohydrate (grammes)
P = Protein (grammes)
F = Fat (grammes)

istic of all the curves obtained. The effect of insulin-tannic acid-zinc is shown in the table and chart to be

Chart showing blood-sugar curves from Case 9; comparing the effects of a single morning injection of insulin-tannic acid-zinc and protamine insulin-zinc with a morning and afternoon injection of ordinary insulin.

similar to that of protamine insulin-zinc in that the single morning dose influences the blood-sugar level throughout the day as effectively as the two doses of ordinary insulin (morning and afternoon). The delay in onset of the hypoglycaemic effect of both protamine and tannic acid mixtures is illustrated, and after twenty-four hours the blood-sugar level remains low. In comparison with the blood-sugar levels obtained after protamine insulin-zinc, those with tannic acid-zinc are on the whole lower and show definitely less fluctuation from the mean. Thus insulin-tannic acid-zinc can effectively replace protamine insulin-zinc in the treatment of diabetic patients. No hypoglycaemic reactions were observed with any of the insulins used.

Skin Reactions

The local effect of hypodermic injection of the insulin-tannic acid-zinc preparation was tried in forty-five patients, including the nine diabetics. After subcutaneous injection of a small dose (10 single units) the site of injection was examined at intervals of a quarter to half an hour, one and a half to two hours, twenty-four and forty-eight hours afterwards. The results are shown in Table II.

TABLE II

Skin Reactions	Time of Onset of Reaction after Injection			
	½-1 hour	1½-2 hours	24 hours	48 hours
Diabetics :				
Positive	1	2	3	1
Negative	8	7	6	8
Non-diabetics :				
Positive	13	16	33	13
Negative	23	20	3	23
Total Reactions :				
Positive	14	18	36	14
Negative	31	27	9	31

"Positive reactions" include erythema, subcutaneous swelling, soreness, and stinging.

The reactions noted were erythema (red wheals from 1 to 4 cm. in diameter), hard tender swellings, stinging and soreness on moving the arm. Thus while soon after injection only fourteen out of forty-five patients showed

any local reaction, after twenty-four hours thirty-six out of forty-five gave evidence of skin irritation. Many stated that they first felt and noticed a reaction about six to eight hours after injection; others experienced the first effects even later (about eighteen to twenty hours after). A further series of hypodermic injections were made with another batch of the preparation on eleven patients, with exactly similar results. One patient was given insulin-tannic acid-zinc daily for about three weeks and showed no such skin reaction and made no complaint throughout the whole of this period.

Conclusion

The delayed but prolonged action of insulin-tannic acid-zinc renders its potential utility in the treatment of diabetic patients comparable to that of the protamine insulin. Thus insulin-tannic acid-zinc may be used successfully in place of protamine preparations in patients who show no cutaneous reactions. Tannic acid is cheap and readily available; thus the cost of the preparation should compare favourably with that of the protamine insulins, which are considerably more costly than ordinary insulin. An objection to the general introduction of insulin-tannic acid-zinc in the proportions used in the present investigation is, however, the occurrence of skin reactions in some patients. In practice it thus becomes essential to give a trial injection to ascertain the sensitivity of the patient before embarking on a course of treatment with the insulin-tannic acid-zinc. Further work on the desirability of altering the composition of the suspension used in the present trials would seem worth while with a view to finding formulae for mixtures less apt to irritate the skin.

Summary

The blood-sugar levels of stabilized diabetic patients were examined after hypodermic injection of insulin-tannic acid-zinc suspension and compared with the levels following the use of protamine insulin-zinc suspensions and ordinary insulin respectively.

A delayed but prolonged hypoglycaemic effect was observed, the potential clinical application of which, however, is offset by its liability to produce irritant skin reactions in some patients.

We are indebted to Mr. W. A. Broom of Boots Pure Drug Co. Ltd. for supplies of the insulin-tannic acid-zinc suspension, and to Professor E. J. Wayne, University of Sheffield, for the interest he has taken in this investigation. Our thanks are also due to Dr. J. Clark, medical superintendent of the City General Hospital, for his permission to use the clinical records.

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W. Van Der Horst (*Nederl. Tijdschr. Geneesk.*, December 18, 1937) records the case of a man, aged 72, who had suffered from prostatic trouble with occasional acute retention for two years. The patient was in a very debilitated state, and refused operation. As no improvement took place after the administration of urinary antiseptics, a catheter was tied in for twenty days, and a male hormone preparation in the form of "neohombreol" in doses of 3 mg. daily was injected. After fourteen injections the catheter was removed, and after ten more injections micturition became normal and painless and general improvement took place. The prostate, though still enlarged, had shrunk to half the size it had been a month previously.