following ischaemia (Stoner and Green, 1947, 1948, 1951), and that the toxic effects of these pentose compounds are strongly potentiated by thromboplastin (Green and Stoner, 1947). We have, however, no direct evidence at all that pentose compounds, thromboplastin, or both are concerned in the mechanism.

Indeed, the pentose compounds are likely to be vaso-depressor and most certainly do not provide the hypertensive agent, the nature of which remains the crux of the problem. The formation of this agent is probably an adaptive mechanism to preserve an adequate blood supply to the placental site. By exclusion the placenta seems to be its most likely source of origin, for ischaemic muscle does not release pressor substances, and the common occurrence of pre-eclampsia when a hydatidiform mole is present excludes the foetus as a source.

Finally, we present some new arguments for the ischaemic theory, arising directly from findings of the Sheffield Traumatic Shock Team. Muscle ischaemia may lead to a profound general interference with carbohydrate utilization. Any superadded disturbance in carbohydrate metabolism strongly increases the harmful effects of the post-ischaemic state. In regions where pellagra and beriberi are endemic the incidence of pre-eclampsia rises steeply, and diabetics are known to be more prone. All these diseases are manifestations of faulty carbohydrate utilization. In striking contrast general undernutrition, as distinct from specific vitamin deficiencies, reduces susceptibility, possibly by diminishing the growth rate of the foetus.

Of the many environmental factors affecting the bodily response to tissue ischaemia, the air temperature is perhaps the most important. A fall of a degree or two may convert a mild into a severe, even fatal, reaction. Though not proved, there is a strong impression that pre-eclampsia occurs most commonly when there is a sudden change to cooler weather.

The direct evidence presented here, supported by such a weight of indirect evidence, strongly favours the ischaemic utero-placental hypothesis. With H. J. Whiteley, experimental work directly testing the hypothesis is in progress, and when this is reported fresh data and points merely mentioned here will be elaborated.

Summary

There was a statistically significant rise in the average pentose and phosphorylated pentose content of the blood plasma in a group of women with pre-eclampsia.

The degree of the rise showed a correlation with the severity of the clinical condition, reaching a peak in frank eclampsia. It had no individual but only a group significance.

It is shown that this rise is probably due to relative utero-placental ischaemia in the pregnant uterus. The hypothesis that this is the proximate cause of pre-eclampsia is now supported by direct evidence. Other facts, some new, are presented which give strong indirect support to this hypothesis.

The nature of the substances which might be released from an ischaemic placenta and/or uterus is briefly considered. The important hypertensive agent, probably derived from ischaemic placenta, has still to be identified.

The Medical Research Council was responsible for the expenses of this investigation. We are indebted to Mr. R. F. Wrighton, of the Department of Social Medicine, Sheffield, for his valuable statistical help, to Dr. H. B. Stoner for his willing collaboration in closely related investigations, and to the late Professor Chisholm and the staff of the Jessop Hospital for Women for their co-operation.

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HYPOGLYCAEMIA IN TREATMENT OF RHEUMATOID ARTHRITIS

BY

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Insulin has been used in three ways in an attempt to improve rheumatoid arthritis: in small dosage to improve metabolism and increase appetite (Copeman, 1931); in conjunction with cortisone in order to attempt to spare protein and to make carbohydrate available at the cell face (Henderson *et al.*, 1951); and to stimulate the pituitary-adrenal complex (Kersley *et al.*, 1950) by means of hypoglycaemia.

In October, 1950, we published a report on the treatment of a pilot series of 40 cases of rheumatoid arthritis with hypoglycaemia. Since this communication 32 further cases have received similar treatment, making a total of 72. All these cases have been followed up for at least two months, and some in which improvement has continued or been maintained, have been followed up for 12 months. Some of the patients who improved at the end of treatment and then relapsed were given a second course of hypoglycaemia. Some of the patients who did not respond

to insulin were given a short course of A.C.T.H. and cortisone, and the clinical response to these hormones was compared with that of another group who improved and later relapsed after hypoglycaemic treatment. A few patients who improved with hypoglycaemia were given minimal doses of these hormones immediately after treatment, in an endeavour to maintain improvement, and were compared with a similar group who received the same dosage of hormones only. As all patients who received treatment were also given a basic regime of rest and physiotherapy in hospital, a series of controls who received this basic regime alone were similarly assessed for comparable periods.

The technique of treatment and the method of clinical assessment were similar to those previously reported. A good hypoglycaemic reaction was indicated clinically by flushing, sweating, weakness, and drowsiness, and the dose required to produce this varied widely, from 16 to 120 units. Some patients were treated for six weeks in order to determine if a change in tolerance to insulin developed, but when once stabilized it was found that little change in dosage for any individual patient was necessary.

Pathological investigations (in addition to routine E.S.R. and Hb) in some cases included estimations of eosinophil counts, potassium and sulphhydryl levels in the serum, 17-ketosteroids and cortin-like bodies in the urine, and the excretion of potassium and phosphate in the urine.

Results

The results are summarized in Table I. Of the 72 cases treated, 82% had improved after treatment, 44% markedly so, but two months later these figures had

deteriorated to 58% and 30% respectively, owing to relapses. Seven of the first 40 cases were greatly improved and appeared to be in complete clinical remission six months after completing treatment. These figures may be compared with a control series of 22 subjects who received physical treatment only in hospital. In this control series, 78% were improved on discharge from hospital, but only 14% markedly so. Two months later the figures were 74% and 32% respectively. In the series treated with hypoglycaemia, those with a history of the disease being present for one year or less reacted slightly better than those of longer duration.

From examination of the Table it may be seen that the increase in weight of the cases whilst under treatment was considerable. 96% of cases gained more than 3 lb. (1.4 kg.) and 6% more than 15 lb. (6.8 kg.). Two months later 79% were more than 3 lb. (1.4 kg.) heavier than before treatment. There was, however, no correlation between improvement and previous loss of weight as has been suggested by the somewhat astonishing gain in weight during treatment in nearly all cases.

There was a tendency to decrease in the sedimentation rate. Immediately after treatment 53% showed a decrease of more than 10 mm. (Westergren) and 27% showed a rise of more than 10 mm. Two months later those with a corresponding fall in E.S.R. were reduced to 43% and those with a corresponding rise increased to 37%.

There did not appear to be any beneficial effect on the haemoglobin levels. Only 20% of cases showed a rise of more than 1 g. per 100 ml., whereas in 43% the haemoglobin fell by more than 1 g. per 100 ml. Two months later the corresponding figures were 35% and 42%.

TABLE I.—*Effect of Three Weeks' Course of Hypoglycaemia on Rheumatoid Arthritis*

Clinical Condition								
	No. of Cases	Complete Remission	Much Improved	Improved	Unchanged	Deteriorated		
At end of treatment ..	72		32 (44%)	27 (38%)	11 (15%)	2 (3%)		
Two months later ..	64	7 (11%)	12 (19%)	18 (28%)	17 (26.5%)	10 (15.5%)		
Effect on Weight								
	No. of Cases	Loss	No Change	+ 3-9 lb. (1.4-4.1 kg.)	+ 9-15 lb. (4.1-6.8 kg.)	+ 15 lb. (6.8 kg.)		
At end of treatment ..	69	1 (1.4%)	2 (2.8%)	38 (55%)	24 (35%)	4 (5.8%)		
Two months later ..	60	4 (6%)	9 (15%)	27 (46%)	16 (27%)	4 (6%)		
Effect on Sedimentation Rate								
	No. of Cases	Decrease			No Change	Increase		
		40	20-40	10-20		10-20	20-40	40
At end of treatment ..	67	4 (6%)	15 (22.5%)	17 (25%)	13 (19.5%)	10 (15%)	5 (7.5%)	3 (4.5%)
Two months later ..	62	4 (6.5%)	9 (14.5%)	14 (22.5%)	12 (19.5%)	8 (13%)	10 (16%)	5 (8%)
Effect on Haemoglobin								
	No. of Cases	Increase			No Change	Decrease		
		4 g.	2-4 g.	1-2 g.		1-2 g.	2-4 g.	4 g.
At end of treatment ..	67	2 (3%)	4 (6%)	7 (10.5%)	25 (37.5%)	16 (23.5%)	9 (13.5%)	4 (6%)
Two months later ..	62	1 (1.5%)	11 (18%)	10 (16%)	14 (22.5%)	12 (19.5%)	13 (21%)	1 (1.5%)
Controls: Clinical Conditions								
	No. of Cases	Complete Remission	Much Improved	Improved	Unchanged	Deteriorated		
At end of treatment ..	22		3 (13.5%)	14 (64%)	4 (18%)	1 (4.5%)		
Two months later ..	19	1 (5.3%)	5 (26.3%)	8 (42.1%)	4 (21%)	1 (5.3%)		

A second course of hypoglycaemia was given to 12 patients who had improved after a first course but had later relapsed after periods varying from 4 days to 13 weeks. Details are given in Table II. The striking

TABLE II.—*Comparison of Results of First and Second Courses of Hypoglycaemia*

Case No.	Duration of 1st Course	Clinical Change After 1st Course	Time Interval of Relapse	State of Relapse	Time Interval Between 1st and 2nd Courses	Duration of 2nd Course	Clinical Change After 2nd Course
2	13 days	++	5 weeks	—	13 weeks	5 days	+
3	13 "	++	4 "	0	13 "	5 "	0
21	20 "	+	8 "	—	15 "	14 "	0
23	20 "	++	13 "	+	18 "	15 "	+ +
26	18 "	++	3 "	—	8 "	20 "	+
33	19 "	++	10 days	0	8 "	15 "	+
38	20 "	++	7 "	0	9 "	10 "	0
40	15 "	++	14 "	0	8 "	15 "	0
51	20 "	++	4 "	0	15 "	30 "	+ +
65	15 "	+	No relapse	—	6 "	30 "	0
69	15 "	+	3 weeks	0	7 "	20 "	0
5	19 "	+	10 "	—	8 months	15 "	+ +

feature is that only six patients improved at all, and of these only three improved as much as or more than with the first course.

During treatment with hypoglycaemia 35 out of 36 cases showed a decrease in the level of circulating eosinophils four and a half hours after maximal hypoglycaemia, as previously reported by us, but there was no clear correlation between this eosinopenia and either the clinical results or the Thorn test with A.C.T.H.

Estimations of the 17-ketosteroid and cortin-like bodies in the urine were carried out on nine cases, but in only one was there an apparent increase in both these steroids, and in one the cortins only.

There appeared to be a significant increase in potassium excretion in the 24-hour specimens of urine in four out of six cases, the average figure being 2.7 g., whereas the average excretion in control periods was 1.57 g. There was also a decrease of more than 50% in the phosphate excretion during the period of hypoglycaemia (but not over a 24-hour period) in four out of the five cases in which this determination was carried out.

The serum potassium was lowered at the height of hypoglycaemia in 34 out of 36 cases, but became normal within four hours. The serum sulphhydryl content did not appear to be affected.

Insulin and A.C.T.H.

An attempt has been made to compare the clinical effects upon individual cases of treatment with hypoglycaemia and A.C.T.H. Three cases which had responded well to insulin and then relapsed, and three cases which had failed to respond to insulin, were each given similar short courses of A.C.T.H. (The usual experimental course consisted of 100 mg. in divided dosage for four days and was then modified as clinically indicated.) From the Chart it will be seen that the three cases (1, 2, and 3) which had responded to insulin reacted excellently to A.C.T.H. Those cases (4, 5, and 6) in which arthritis had not improved with insulin in hypoglycaemic dosage responded poorly or not at all to A.C.T.H. In one case (No. 5) which had deteriorated during insulin treatment there was no response when the dose of A.C.T.H. was raised to 400 mg. daily, but every

case except one (Case 6) responded to cortisone. Four cases which had responded to hypoglycaemia were immediately given 20 mg. of A.C.T.H. daily and one improved still further and two retained their improvement. Four similar cases which had not received insulin had a similar course of A.C.T.H., two improving very slightly.

Discussion

No definite conclusions can be drawn from our findings on the mode of action of hypoglycaemia in rheumatoid arthritis, but in this connexion the work of Vogt (1950) may be quoted. She found that only A.T.P. or a very high concentration of potassium was effective in stimulating the perfused adrenal cortex isolated from pituitary effect. Adrenaline, which is produced by hypoglycaemia, has been shown experimentally to stimulate A.C.T.H. production, but clinically the results have not been dramatic, though Bliss *et al.* (1951) showed interesting results in normal subjects. After denervation of the adrenals, Vogt has shown that hypoglycaemia will still cause increased production of A.C.T.H., possibly through a second mechanism of reduction of circulating corticoids.

In our cases the marked reduction of circulating eosinophils in nearly all cases suggests pituitary-adrenal stimulation; the changes in potassium levels and excretion are compatible with this hypothesis, and we feel that the steroid excretion results do not rule this out.

Comparison of the figures of very marked improvement directly after treatment (44%) and two months later (30%) with those in the control series (14% and 32%) is such as one might expect with the use of medium doses of A.C.T.H. Again, the fact that the degree of clinical response to insulin corresponded very closely to the response to A.C.T.H. suggests that hypoglycaemia may have a pituitary-stimulating effect.

From the practical point of view we feel that hypoglycaemic therapy, although more difficult to administer than A.C.T.H. treatment, has much the same advantages and disadvantages, except that it is doubtful whether the response obtained by larger doses of A.C.T.H. can be obtained. This "treatment" may therefore be regarded as having a limited practical value in tiding over a temporary relapse, particularly if this has been occasioned by some temporary or removable factor and in conjunction with other methods in getting some mild cases back to work. In such cases it may produce a complete remission, as occurred in seven out of our first 40 cases so treated.

It is obviously not applicable in the third practical role of A.C.T.H. in rheumatoid arthritis—that is, tiding over surgical and manipulative intervention.

Summary

Of 72 cases treated by hypoglycaemia 82% were temporarily improved, 44% markedly so. The improved figure had dropped to 58% in two months, but seven had progressed to complete remission after six months.

In a control series, without insulin therapy, 78% improved on a similar hospital regime but only 14% markedly.

A second course of treatment had less effect than the first.

Gain in weight was considerable and occurred in all but three cases; there was a tendency to improvement in the sedimentation rate but not in the haemoglobin level.

Reduction in circulating eosinophils occurred almost without exception. Observations on changes in potassium, phosphate, and steroid excretion were made.

COMPARISON OF THE CLINICAL EFFECTS OF
INSULIN WITH A.C.T.H. AND CORTISONE

The clinical response to hypoglycaemia was compared with subsequent A.C.T.H. treatment and was found to correlate closely.

The possible mechanism and practical value of hypoglycaemic therapy in rheumatoid arthritis are discussed.

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SPONTANEOUS HYPOGLYCAEMIA AFTER INSULIN THERAPY IN RHEUMATOID ARTHRITIS

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We have previously reported the effects of insulin hypoglycaemia upon rheumatoid arthritis (Kersley *et al.*, 1950). Of 80 patients treated, two developed attacks of spontaneous hypoglycaemia shortly after therapy ended. This complication is not mentioned by Sargant and Slater (1948) in discussing the use of hypoglycaemic therapy in mental disease. Our two cases were therefore thought to be worthy of a brief report.

Case 1

A married woman aged 36 had a four-months history of rheumatoid arthritis affecting the hands, feet, and knees. Her general health was quite good. No special treatment had been given. She had had rheumatic fever at 32. Her mother and two uncles have rheumatoid arthritis.

On examination grip was poor in both hands, and there was swelling and tenderness of all proximal interphalangeal joints, with slight limitation of movement at the right wrist and pain on passive flexion of the toes. General clinical examination otherwise showed no abnormality, apart from a blowing apical systolic murmur without cardiac enlargement. Her weight was 118 lb (53.5 kg.); E.S.R. 44 mm. in one hour (Westergren); haemoglobin 49%; fasting blood sugar 105 mg. per 100 ml.

Insulin Therapy

Insulin therapy was given for 13 days, and hypoglycaemic reactions occurred on 10 days with doses of 24 to 38 units of soluble insulin. After treatment her general health was much improved and pain and stiffness in the joints were considerably reduced. The haemoglobin and E.S.R. levels were virtually unchanged. Her weight had risen by 6 lb. (2.7 kg.). The fasting blood sugar one week after the end of treatment was 100 mg. per 100 ml. The improvement lasted for about five weeks, but after a further month the

condition had relapsed to a state slightly worse than before treatment.

Three months after the end of the first course a second course of hypoglycaemia was given, lasting five days, on four of which good reactions occurred with doses of 32 to 44 units of insulin. Some improvement in joint pain and stiffness resulted, though this was less than on the previous occasion. It was hoped to maintain this improvement by giving single weekly hypoglycaemic reactions. Therefore one week after the end of the second course 36 units of insulin was given but no reaction followed. One week later (August 9, 1950) she reported again, but insulin was not given, as she had had diarrhoea and nausea for four days. She returned home and the diarrhoea settled in two to three days. On August 14 she had a slight pyrexia of undetermined cause.

On August 15, 12 days after the last dose of insulin, the patient's husband awoke at about 3 a.m. to find her sitting up in bed in a delirious condition, which lasted four hours and was followed by spontaneous sleep. The patient had no memory of the attack, and appeared normal when seen by her doctor at 11 a.m. Attacks occurred daily until her admission on August 19, but appeared a little later each successive day and became less severe. On August 20 an attack, characterized by vertigo, blurred vision, weakness of the limbs, sweating, and shivering, started at 7.20 a.m. After 6 oz. (170 g.) of glucose by mouth she rapidly recovered. On August 21 she had mild diplopia and right-sided weakness at about 9.30 a.m., when the fasting blood sugar was found to be 23 mg. per 100 ml. Mild attacks occurred before breakfast on August 22, 23, and 24. A high-protein diet was then given and a milk drink at 10 o'clock each night. No further attacks occurred, and the patient was discharged on August 29.

Investigations

On August 22, 19 days after the conclusion of insulin treatment and seven days after the first attack of spontaneous hypoglycaemia, the glucose-tolerance curve showed:

9 a.m. (fasting) blood sugar	..	=	40 mg. per 100 ml.
50 g. of glucose given			
After $\frac{1}{2}$ hour blood sugar	..	=	40 " " " "
" 1 hour " "	..	=	66 " " " "
" 2 hours " "	..	=	166 " " " "
" 3 hours " "	..	=	71 " " " "
No glycosuria occurred.			

9 a.m.: Plasma alkaline phosphatase, 2 units; plasma bilirubin, less than 0.2 mg. per 100 ml.; serum colloidal gold reaction, 3; thymol turbidity, 2.5 units; serum potassium, 15 mg. per 100 ml.; blood urea, 28 mg. per 100 ml.; eosinophils (direct count), 55 per c.mm. 12 noon: Eosinophils, 0. 2 p.m.: Eosinophils, 28 per c.mm.; serum potassium, 17.3 mg. per 100 ml.

Case 2

A woman aged 43 had a 12-years history of slowly progressive rheumatoid arthritis; most joints were involved. Her general health was fair. She had had physiotherapy but no gold.

Examination showed her to be frail, her weight being 78 lb. (35.4 kg.). The mucosae were pale. There were marked rheumatoid changes in hands, feet, ankles, wrists, elbows, shoulders, and knees. No abnormality was found in the heart, lungs, abdomen, or C.N.S. The E.S.R. was 59 mm. in one hour (Westergren); haemoglobin 58%; fasting blood sugar 100 mg. per 100 ml.

Insulin Therapy

Insulin therapy was given for 20 days, hypoglycaemic reactions occurring on 15 days with doses of 20 to 38 units of insulin. On the day when the latter dose was given treatment had to be interrupted by administering intravenous glucose because of the onset of coma.