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.

We would like to express our appreciation of the help given by the nursing and laboratory staff of the Royal National Hospital for Rheumatic Diseases, and of the grant made by the Empire Rheumatism Council towards laboratory expenses.

REFERENCES

- Bliss, E. L., *et al.* (1951). *J. clin. Endocrinol.*, **11**, 46.
 Copeman, W. S. C. (1931). *British Medical Journal*, **2**, 1130.
 Henderson, E., *et al.* (1951). *J. clin. Endocrinol.*, **11**, 119.
 Kersley, G. D., *et al.* (1950). *British Medical Journal*, **2**, 855.
 Vogt, M. (1950). *Ibid.*, **2**, 1242.

SPONTANEOUS HYPOGLYCAEMIA AFTER INSULIN THERAPY IN RHEUMATOID ARTHRITIS

BY

G. D. KERSLEY, M.D., F.R.C.P.

L. MANDEL, M.B., M.R.C.P.

K. B. TAYLOR, B.M., M.R.C.P.

AND

M. R. JEFFREY, M.B., M.R.C.P.

(From the South-west and Oxford Regional Rheumatism Research Unit, Royal National Hospital for Rheumatic Diseases, Bath)

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.

After treatment there was some improvement in her general health, and her weight had risen by 5 lb. (2.3 kg.). The joints were generally less painful and stiff, but there was no objective change on examination. Three days after the end of treatment the fasting blood sugar was 50 mg. per 100 ml.; E.S.R. 70 mm. in one hour; haemoglobin 67%. The subjective improvement lasted about two months, and then relapse occurred to a state slightly worse than before insulin therapy.

Four months after the first, a second course of insulin was given, lasting 13 days, on seven of which a good reaction occurred. This course again produced some subjective improvement but no objective change. On November 10, 1950, the day after the last insulin treatment, the patient was found to be sweating and incoherent at 6 a.m., and was later incontinent of urine. She revived after oral glucose was given. On November 12 a similar attack took place and was again terminated by oral glucose. In this second attack the blood sugar was 38 mg. per 100 ml. Only one further attack occurred, 10 days later at 1 p.m. after an overnight fast and towards the end of a hippuric-acid test.

It later transpired that this lady usually took a milky drink at 9.30 p.m.; on both the evenings preceding the hypoglycaemic attacks she had not taken this drink.

Investigations

The last insulin treatment was given on November 9, and spontaneous hypoglycaemic attacks occurred on November 10, 11, and 12.

November 10-11.—Total neutral 17-ketosteroids, 6.2 mg. per 24 hours; cortins, 2 mg. per 24 hours.

November 11.—Glucose-tolerance curve:

Fasting blood sugar	..	..	= 74 mg. per 100 ml.
50 g. of glucose given			
After ½ hour blood sugar	..	= 125	" " " "
" 1 " "	" "	= 142	" " " "
" 1½ hours "	" "	= 166	" " " "

Unfortunately no further specimens were taken.

November 11-12.—Total neutral 17-ketosteroids, 5.4 mg. per 24 hours; cortins, 1.75 mg. per 24 hours.

November 13.—Insulin-sensitivity test:

Fasting blood sugar	..	..	= 23 mg. per 100 ml.
5 units of soluble insulin given intravenously			
After 20 mins. blood sugar	..	= 27 mg. per 100 ml.	
" 30 " "	" "	= 23	" " " "
" 45 " "	" "	= 40	" " " "
" 60 " "	" "	= 43	" " " "
" 90 " "	" "	= 40	" " " "
" 120 " "	" "	= 31	" " " "
Adrenaline hydrochloride given, 0.4 mg. intramuscularly			
After 45 mins. blood sugar	..	= 33 mg. per 100 ml.	
" 60 " "	" "	= 31	" " " "

November 14.—Glucose-tolerance test:

Fasting blood sugar	..	..	= 44 mg. per 100 ml.
50 g. of glucose given			
After ½ hour blood sugar	..	= 91	" " " "
" 1 " "	" "	= 105	" " " "
" 2 hours "	" "	= 111	" " " "
" 3 " "	" "	= 64	" " " "
" 4 " "	" "	= 25	" " " "

November 15.—A.C.T.H. test: eosinophils, 9 a.m., 70 per c.mm.; 25 mg. of A.C.T.H. given intramuscularly; eosinophils, 1 p.m., 36 per c.mm.

November 16.—Control eosinophils: 9 a.m., 56 per c.mm.; 1 p.m., 95 per c.mm. Total neutral 17-ketosteroids, 8.7 mg. per 24 hours; cortins, 1.9 mg. per 24 hours.

November 23.—Oral hippuric acid synthesis test: 4 g. of sodium benzoate given; three hourly specimens of urine secured; the fourth hourly specimen could not be collected owing to a hypoglycaemic attack. In the three-hours urine collection (volume 900 ml.) 2.84 g. of sodium benzoate was excreted as hippuric acid.

November 24.—Insulin-sensitivity test:

Fasting blood sugar	..	..	= 47 mg. per 100 ml.
5 units of insulin given intravenously			
After 20 mins. blood sugar	..	= 22 mg. per 100 ml.	
" 30 " "	" "	= 58	" " " "
" 45 " "	" "	= 58	" " " "
" 60 " "	" "	= 58	" " " "
" 90 " "	" "	= 47	" " " "
" 120 " "	" "	= 41	" " " "
0.4 mg. of adrenaline hydrochloride given			
After 45 mins. blood sugar	..	= 41	" " " "
" 60 " "	" "	= 33	" " " "

November 28.—Oral galactose-tolerance test: 7.3 g. of galactose excreted in five hours after dose of 40 g.

November 29.—Laevulose-tolerance test: fasting blood sugar, 74 mg. per 100 ml.; blood sugar, one hour after test, 116 mg. per 100 ml.

December 7.—Fasting blood sugar, 80 mg. per 100 ml.

December 9.—Fasting blood sugar, 100 mg. per 100 ml.

December 11.—Glucose-tolerance test:

Fasting blood sugar	..	..	= 95 mg. per 100 ml.
50 g. of glucose given			
After ½ hour blood sugar	..	= 190	" " " "
" 1 " "	" "	= 200	" " " "
" 2 hours "	" "	= 142	" " " "
" 3 " "	" "	= 54	" " " "

Six Other Cases

In view of the occurrence of these two cases of spontaneous hypoglycaemia, six cases of rheumatoid arthritis which had received courses of insulin hypoglycaemia had daily blood-sugar estimations carried out for 10 days after cessation of treatment. The results of these tests are plotted in the accompanying Chart. In three cases

Chart showing changes in fasting blood-sugar levels in six cases following insulin treatment.

there was a tendency to initial fasting hypoglycaemia followed by a drop in blood sugar, maximal about the tenth day, and then a rapid return to normal values.

Comment

The occurrence of frank attacks of spontaneous hypoglycaemia after insulin therapy is not common; these two cases are the only examples seen in the 80 cases of

rheumatoid arthritis to which we have now given insulin. It may be significant that in both cases the attacks followed a second course of insulin: we have now given second courses to 12 patients.

In Case 1 the attacks did not begin until 12 days after the last insulin treatment, the patient having suffered meanwhile from gastro-enteritis. The investigations done when she was readmitted did not elucidate the mechanism of the hypoglycaemia. It may be noted, however, that the glucose-tolerance curve suggested slow absorption; that the adrenal response to hypoglycaemia, as judged by subsequent eosinophil depression, was normal; and that the serum colloidal gold reaction was positive (3), thymol turbidity, alkaline phosphatase, and plasma bilirubin being normal.

In Case 2 the spontaneous hypoglycaemic attacks started on the day after the last insulin treatment and must be wholly attributed to the therapy. Evidence of undue sensitivity to the hypoglycaemic action of insulin was sought three days after the first spontaneous attack. In fact, five units intravenously produced no depression at all of the very low fasting blood sugar; neither did adrenaline, given later, produce any rise. Glucose tolerance on the following day was apparently normal, though the curve was pitched at a low level owing to the subnormal fasting blood sugar. One day later 25 mg. of A.C.T.H. produced normal depression of circulating eosinophils.

Several liver-function tests were done between 10 and 15 days after the first spontaneous attack. The oral hippuric-acid synthesis test was probably normal, laevulose tolerance was at the outside limit of normal, and galactose tolerance was distinctly abnormal. A second insulin-sensitivity test was also done at this time. This showed a normal blood-sugar depression 20 minutes after 5 units of insulin intravenously; the depression had, however, been abolished 10 minutes later. Adrenaline was again without any effect at all.

One month after the first attack the fasting blood sugar was normal and the glucose-tolerance curve was of the "lag" type.

From the clinical aspect, the attacks were easily controlled by the institution of a high-protein diet with a "snack" at bedtime. It would seem wise to insist on these measures for three weeks after any course of insulin therapy, for the attacks, though not serious, are distressing to patients and their relations.

Summary

Two cases of rheumatoid arthritis developed attacks of spontaneous hypoglycaemia in the early morning shortly after the end of second courses of insulin hypoglycaemic therapy. The attacks were controlled by a high-protein diet with a feed at bedtime, and the tendency to them disappeared within two weeks.

In six other patients who had received similar treatment, daily fasting blood-sugar estimations for 12 days after stopping insulin administration showed that the lowest blood sugars occurred about the tenth day.

We would like to express our appreciation to Dr. H. J. Gibson and his laboratory staff for some of the pathological investigations, and to Dr. P. Woolf for assistance.

REFERENCES

- Kersley, G. D., *et al.* (1950). *British Medical Journal*, **2**, 855.
Sargant, W., and Slater, E. (1948). *An Introduction to Physical Methods of Psychiatry*, 2nd ed. Livingstone, Edinburgh.

THE NEUROLOGICAL ORIGIN OF PEPTIC ULCER

FRONTAL-LOBE LESIONS AND GASTRIC ULCER

BY

J. L. ARTETA, M.D.

Pathologist, Institute of Medical Pathology, Madrid

There are many reasons, mainly experimental, for belief in the existence of a cortical relation to visceral sensitivity. As Fulton (1943) has said, in the vegetative nervous system, just as in the somatic nervous system, there exist suprasegmental levels capable of influencing intersegmental autonomic reflexes.

The work of Watts and Fulton (1934) and of Davey (1949) has shown the existence of areas in the cerebral cortex whose stimulation or ablation causes changes in the behaviour of the gastro-intestinal tract. These changes are in the motility and secretions of the stomach and intestinal tract.

Cortical relationship to the alimentary tract is confined to the frontal lobes. Stimulation of the sixth area of the frontal lobes in monkeys (Watts and Fulton, 1934) has resulted in an increase of intestinal peristalsis to the extent of obstruction due to intussusception. Davey (1949) obtained similar results with operations on this area, but according to him it is the ocular region of the cortex which reacts best, producing more active changes in the behaviour of the stomach and intestines.

Anatomical evidence has also furnished further proof of these facts. Gastric or intestinal ulceration is often found in experimental animals subjected to cerebral operations. Mettler *et al.* (1936) frequently found gastro-intestinal ulceration in decorticated animals. The earliest account in the literature is that of Brown-Séquard (1876), who reported a perforated gastric ulcer in a dog whose frontal lobes he had cauterized.

There is plenty of clinical evidence to support the relation between the cerebral cortex and the digestive tract. It is well known that in some subjects strong emotions can produce intestinal disturbances due to disorders of motility; the alimentary character of the aura of some epileptic attacks; and the digestive disturbances, usually intestinal, which occasionally occur in leucotomy cases. Among the most significant observations on this subject is a case described by Cushing (1932). Despite the fact that he maintained the view that in those cases in which the gastric lesion had a neurological origin this was to be referred to the hypothalamus, as it is here that vegetative functions are represented and integrated, his case may well be cited. In Cushing's case there were found at post-mortem examination multiple superficial bleeding ulcers in the stomach and duodenum, and in the brain the remainder of a meningioma, previously removed, situated in the olfactory groove, together with a large area of softening in the frontal lobe caused by ligation of the anterior communicating cerebral artery.

Bodechtel (1935) in one of his cases found a glioblastoma multiforme of the frontal lobe and multiple acute bleeding ulcers of the stomach.

I have been able to study post mortem two cases of frontal-lobe lesions associated with multiple acute ulcerations in the stomach and duodenum that may be