Sir Jack Drummond, F.R.S., of Boots Pure Drug Co., Ltd.; and pregnenolone and pregnadienolone by Dr. B. M. Merriman, of British Drug Houses Ltd. Other substances, including material for controls, were kindly supplied by the following firms: Messrs. Allen and Hanburys Ltd., Bayer Products Ltd., Bengel Laboratories Ltd., Ciba Laboratories Ltd., and Roche Products Ltd.

REFERENCES

- Alexander, W. R. M., and Duthie, J. J. R. (1950). *Lancet*, **1**, 297.
 Baehr, G., and Soffer, L. J. (1950). *Bull. N.Y. Acad. Med.*, **26**, 229.
 Boland, E. W. (1950). *Ann. rheum. Dis.*, **9**, 1.
 — and Headley, N. E. (1949). *J. Amer. med. Ass.*, **141**, 301.
 Callow, N. H., Callow, R. K., and Emmens, C. W. (1938). *Biochem. J.*, **32**, 1312.
 Carlisle, J. M. (1950). *British Medical Journal*, **2**, 590.
 Corcoran, A. C., and Page, I. H. (1948). *J. Lab. clin. Med.*, **33**, 1326.
 Davison, R., Koets, P., Snow, W. G., and Gabrielson, L. G. (1950). *Arch. intern. Med.*, **35**, 365.
 Freeman, H., Pincus, G., Johnson, C. W., Bachrach, S., McCabe, G. E., and MacGilpin, H. (1950). *J. Amer. med. Ass.*, **142**, 1124.
 Freyberg, R. H. (1950). *Bull. N.Y. Acad. Med.*, **26**, 206.
 Guest, C. M., Kammerer, W. H., Cecil, R. L., and Berson, S. A. (1950). *J. Amer. med. Ass.*, **143**, 338.
 Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
 — (1950). *Arch. intern. Med.*, **85**, 545.
 Ishmael, W. K., Hellbaum, A., Kuhn, J. F., and Duffy, M. (1949). *J. Okla. med. Ass.*, **42**, 434.
 Mason, H. L., Myers, C. S., and Kendall, E. C. (1936). *J. biol. Chem.*, **116**, 267.
 Quin, C. E., Mason, R. M., and Knowelden, J. (1950). *British Medical Journal*, **2**, 810.
 Reichstein, T. (1936). *Helv. chim. Acta*, **19**, 1107.
 Sommerville, I. F., Gough, N., and Marrian, G. F. (1948). *J. Endocrinol.*, **5**, 247.
 — Marrian, G. F., Duthie, J. J. R., and Sinclair, R. J. G. (1950). *Lancet*, **1**, 116.
 Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). *Arch. intern. Med.*, **85**, 199.
 Stock, J. P. P., and McLure, E. C. (1950). *Lancet*, **2**, 125.
 Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Roche, M., Staehelin, D., and Wilson, D. L. (1950). *New Engl. J. Med.*, **242**, 783.
 Venning, E. H. (1948). *Med. Clin. N. Amer.*, **32**, 89.
 Wintersteiner, O., and Pfiffner, J. J. (1936). *J. Biol. Chem.*, **116**, 291.

A "Brochure of Instruments and Accessories for Radio-isotope Applications" has just been issued by the Scientific Instrument Manufacturers Association (of Great Britain, Ltd.) in collaboration with the Atomic Energy Research Establishment, Harwell. It is likely to be a useful booklet for all interested in employing radio-isotopes in their work, since it is in effect a directory to all instrument manufacturers, to consultants capable of advising in work of this kind, and to the suppliers of radio-isotopes (at Harwell and at the Radiochemical Centre, Amersham), as well as providing a short discussion on the kinds of instruments to be employed in different situations. Thus Geiger-Müller counters may register either the total radiation they receive in a given time or the rate at which they receive it; they may be sealed off or have an arrangement for introducing the substance to be assayed for radioactivity actually into the counter tube. Scintillation counters contain phosphors which sparkle as gamma rays strike them, and a device for counting the flashes. Ionization chambers measure in a given time the total radiation due to nuclear particles striking the atoms of gas in the chamber. Several kinds of instruments are available for health monitoring. A small direct-reading ionization chamber set in a fountain-pen-like cylinder measures the cumulative exposure to radiation of the person who wears it in his pocket. A hand-and-foot monitor looks something like a weighing-machine, on which the person under examination stands. Under its platform are two G.-M. counters, which measure the radiation from dirt on the shoes, while at arm height are pockets into which the hands can be thrust to have their radioactivity assayed by further adjacent counters. Two frisking probes are counters attached to the sides of the machine by long flexible leads. It is interesting to note that no less than six different firms make G.-M. counters, and eight produce monitoring instruments. In addition to the official isotope information office at Harwell there are also three private firms of consultants in this field of work. Copies of the brochure can be obtained free of charge from the publishers.

INSULIN AND E.C.T. IN TREATMENT OF RHEUMATOID ARTHRITIS

REPORT ON A PILOT SERIES OF CASES

BY

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

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

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

M. H. L. DESMARAIS, M.R.C.S., L.R.C.P., D.Phys.Med.

AND

E. BENE, M.D.

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

Insulin has been used as a "tonic" and as a method of increasing weight in rheumatoid arthritis for a number of years (Copeman, 1931). The more recent theories of the part played by the pituitary adrenal mechanism in this disease have suggested another reason for this type of therapy. Cannon *et al.* (1924) found that insulin hypoglycaemia provoked the liberation of adrenaline, and since then evidence has been produced which is claimed to show that the adrenal cortex can be stimulated in this way, either directly in hypophysectomized animals or indirectly by stimulation of the pituitary with liberated adrenaline (Langecker, 1928; Miller *et al.*, 1941; Godlowski, 1947). It seemed that this explained the benefit obtained from insulin shock therapy and electric convulsion therapy (E.C.T.) in many mental disorders. Moreover, it had been noted that the combination of rheumatoid arthritis and epilepsy was extremely rare. On the suggestion of one of us (M. H. L. D.) it was decided to treat a pilot series of cases of active rheumatoid arthritis with insulin hypoglycaemia and a second series with E.C.T., and observe the clinical and biochemical results.

Methods and Techniques

All patients were suffering from active rheumatoid arthritis, and in addition to insulin therapy all received the same basic regime of treatment, which included rest splints, remedial exercises, and physiotherapy. Treatment was not begun until patients had had two weeks' basic physical treatment in hospital.

The method used was based on the modified insulin technique as described by Sargent and Slater (1948). Attempts were made to induce hypoglycaemic reactions every morning for five days each week, leaving Saturday and Sunday free of treatment. Treatment was carried out over a period of three or four weeks. A good hypoglycaemic reaction was indicated by marked flushing and sweating, weakness, drowsiness, and tremor. The reaction was normally interrupted three hours after the dose of insulin by a meal containing 16 oz. (454 g.) of mashed potatoes flavoured with an egg, or other suitable breakfast dish, together with bread-and-butter, jam, porridge, and sugared tea. Only if the patient went into sopor or coma, or had convulsions, was hypoglycaemia interrupted earlier by intravenous glucose. This had to be carried out in four patients (Cases 21, 23, 30, 33).

Patients were assessed clinically every week, before, during, and just after treatment, and also at varying periods after treatment was completed. The assessment included observations on the general feeling of well-being, mental outlook, subjective pain (including rest pain),

stiffness, swelling, range of movement, deep hyperalgesia, in addition to functional ability—e.g., ability to dress, shave, brush the hair, walk, use a knife and fork. Patients were also weighed weekly before, during, and after treatment, before breakfast, and after emptying the bladder and, if possible, bowels.

In view of the rapid increase in weight during and the decrease after treatment, fluid balances were performed latterly before and after treatment.

During the week before starting treatment, estimations of sedimentation rate (E.S.R.), haemoglobin, haematocrit, fasting blood sugar, and serum potassium were carried out. Urinary uric acid and creatinine levels were estimated on a 24-hour specimen in all cases and 17-ketosteroids in 8 cases (Nos. 8, 10, 17, 18, 23, 24, 25, 26). In addition the basic level of circulating eosinophils was ascertained under strict standard conditions (see below), together with changes of such levels in response to injections of adrenaline and A.C.T.H.

During treatment, on the first day on which the patient showed a good hypoglycaemic reaction, similar controlled estimations of eosinophil counts, serum potassium, blood sugar, and urinary uric acid and creatinine levels were carried out. The same tests were repeated during the week following completion of treatment.

The "activity index" referred to in Tables I and II represents an attempt to give a numerical value to the activity of the disease. The index is derived from four factors—change in weight, E.S.R., haemoglobin levels, and degree of pain at rest. These are graded on a three-point scale, as explained in a previous paper (Kersley *et al.*, 1950).

Blood sugars were estimated by the method of Folin and Wu, and urinary uric acid and creatinine by Folin's method.

TABLE I

Case No.	Age and Sex	Duration of Disease (Years)	Duration of Treatment (Days)		Min. Dose Insulin to Produce Hypoglycaemia (Units)	Clinical Degree of Hypoglycaemia	Clinical Change	Change in Activity Index
			Total	Effective				
1	38 F	$\frac{1}{2}$	13	10	20	Marked	++	+2
2	35 F	$\frac{1}{2}$	13	10	32	"	++	0
3	31 F	$\frac{1}{2}$	13	10	28	"	++	+1
4	53 F	2	13	0	60	Nil	0	-1
5	30 F	20	19	12	44	Moderate	+	+2
6	21 F	$1\frac{1}{2}$	15	11	32	Marked	0	+2
7	58 F	$\frac{1}{2}$	9	6	24	Moderate	0	+1
8	54 F	$1\frac{1}{2}$	15	11	24	Marked	+	+4
9	52 M	$\frac{1}{2}$	19	17	40	"	++	+3
10	64 M	$\frac{1}{2}$	15	1	112	"	0	+1
11	50 M	10	19	7	108	Slight	+	0
12	21 M	5	26	10	72	Moderate	0	+2
13	45 M	$1\frac{1}{2}$	20	15	52	Marked	++	-1
14	22 F	1	20	16	36	"	++	-1
15	62 M	$1\frac{1}{2}$	19	16	24	"	0	+2
16	68 M	$5\frac{1}{2}$	19	10	64	Moderate	+	0
17	45 F	$\frac{1}{2}$	19	17	32	Marked	0	0
18	47 F	2	19	17	24	"	++	+3
19	65 M	12	20	17	40	"	++	+1
20	54 M	18	20	16	48	"	-	+2
21	43 F	12	20	15	20	"	+	+1
22	41 F	2	20	18	30	"	++	+3
23	42 F	2	20	7	88	"	++	0
24	57 M	$\frac{1}{2}$	20	17	48	"	++	+2
25	56 F	2	20	12	64	"	++	+1
26	58 M	6	18	13	48	"	++	+3
27	50 F	$3\frac{1}{2}$	15	13	24	"	++	+2
28	55 F	2	15	13	24	"	++	+3
29	46 F	2	15	13	36	"	++	+2
30	45 M	3	19	15	48	"	+	0
31	32 F	$1\frac{1}{2}$	15	14	16	"	++	+2
32	55 M	10	19	6	108	Slight	+	+2
33	50 M	4	19	16	48	Marked	++	+2
34	45 M	$1\frac{1}{2}$	19	12	52	Moderate	+	0
35	40 M	$\frac{1}{2}$	14	11	48	Marked	+	+2
36	40 F	10	13	12	24	"	++	0
37	48 F	$1\frac{1}{2}$	19	18	32	"	++	+1
38	21 F	5	20	17	52	"	++	+1
39	36 M	$1\frac{1}{2}$	19	5	64	"	0	+2
40	38 F	14	15	12	68	"	++	+2

Clinical change: - = Deterioration. 0 = No change. + = Slight improvement.
++ = Marked improvement.

During the latter period of these observations total neutral 17-ketosteroids were estimated in the urine by the modified method of Callow *et al.* (1938), where creatinine levels of the 24-hour urine specimens were constant.

Serum potassium estimations were carried out by the method of King (1946). These tests were done before treatment was started (fasting) and on the first day of definite clinical hypoglycaemic reaction, both at 10 a.m. (at the height of hypoglycaemia) and at 3 p.m. (when the eosinopenic response was maximal).

Circulating eosinophils were counted by the Randolph (1949) technique, four improved Neubauer chambers being used. Three o'clock was chosen for the time of the second eosinophil count because we ascertained by preliminary observations that the maximal eosinophil depression occurred about that time, the figure varying little between 2 p.m. and 3.30 p.m. The count was thus made about $4\frac{1}{2}$ hours after the ending of hypoglycaemia by breakfast. The counts are given in Table II. In addition to the counts observed, the 3 p.m. figure was expressed as a percentage of the 10 a.m. value (columns 3 and 6); the ratio of the "hypo. day" to the "control day" represents the true depression consequent upon hypoglycaemia. Cases 1-4 did not have an adequate control estimation; all of them, however, showed considerable eosinophil depression after hypoglycaemia.

Results and Observations

Of 40 cases (17 male and 23 female) in whom treatment has been completed, 22 (55%—6 male and 16 female) showed marked clinical improvement, 9 (22.5%—6 male and 3 female) showed slight clinical improvement, and 8 (20%—4 male and 4 female) showed no significant change. One patient (Case 20) deteriorated (see Tables).

In most cases in which there was marked clinical improvement, such improvement occurred after the first week's treatment (shortly after a hypoglycaemic reaction was obtained) and continued throughout the whole course. Improvement was pronounced in all aspects, especially in general feeling of well-being and mental outlook, with loss of malaise and increase of appetite, lessening of pains in joints (including rest pain), and deep hyperalgesia. The general impression was that the joints of the upper limbs improved more than those of the lower limbs, and that joints more recently affected showed an earlier and more marked response than the others.

In those patients only slightly improved, improvement affected some joints but not others, and the patient's condition often varied throughout treatment. Although there was frequent subjective improvement, objective change was not significant.

Of the 8 patients in whom there was no change, one (Case 7) had had treatment for only nine days, when therapy had to be stopped because the hypoglycaemia was causing her to become mentally confused and irrational; in another (Case 17), though the pains in the upper limbs improved very slightly, the knees flared up during treatment.

All patients showed a gain in weight. The mean initial weight for men was 133 lb.—range 105–170 lb.—(60.3 kg.; range 47.6–77.1 kg.) and for women was 111 lb.—range 78–165 lb. (50.3 kg.; range 35.4–74.8 kg.). The mean increase in weight for men was 7 lb.—range 1–15 lb.—(3.17 kg.; range 0.45–6.8 kg.) and for women 6 lb.—range 2–11 lb.—(2.72 kg.; range 0.9–4.99 kg.).

All the 22 cases showing marked clinical improvement had quite definite and pronounced hypoglycaemic reactions

clinically. Of the 9 cases which had slight clinical improvement, 4 had marked, 3 had moderate, and 2 had slight hypoglycaemic reactions. Of the 8 cases which showed no significant clinical change, 5 had marked, 2 had moderate, and 1 had no hypoglycaemic reaction.

Of the 22 cases which showed pronounced clinical improvement, 15 had had the disease for three years or less and 7 for over three years. Those patients with slight or no clinical improvement fell equally into these two duration groups.

There was no obvious change in the sedimentation rates during treatment.

Of 39 cases, 14 (36%) showed an increase of more than 1 g./100 ml. Hb, 3 a decrease of more than 1 g./100 ml.,

values 4½ hours later in all cases. In 34 cases the potassium level was lowered during hypoglycaemia by amounts ranging from 0.8 to 9.4 mg./100 ml.; in one case the value was unaltered and in another case it rose by 3.3 mg. (Cases 34 and 20 respectively). In the cases showing a fall the mean control value was 19.8 mg. and the hypoglycaemic value 15.9 mg., the mean fall being 3.9 mg./100 ml. (20%). The lowest figure recorded was 13.0 mg.

At the time of maximal eosinopenia (3 p.m.) the mean potassium level had risen to 20.9 mg.—i.e., 1.1 mg. above the control value. Some increase above the hypoglycaemic level was present in every case: in 13 cases the control value was exceeded by more than 1 mg./100 ml., the highest figure recorded being 27.5 mg.

TABLE II

No.	Eosinophils							Potassium			Sugar		Adrenaline Test	A.C.T.H. Test	U.A./Cr. Ratio	Clinical Change*	Change* in Activity Index
	Control			Hypoglycaemic			True Depression 100 — (6)/(3)%	Control	Hypoglycaemic		Fasting	Hypoglycaemic					
	10 a.m. (1)	3 p.m. (2)	(2)/(1)% (3)	10 a.m. (4)	3 p.m. (5)	(5)/(4)% (6)			10 a.m. (7)	3 p.m. (8)							
1	—	—	—	117	55	47	—	20.8	17.6	21.2	83	50	Neg.	—	+	++	+2
2	—	—	—	405	183	45	—	18.2	13.9	21.4	100	50	Pos.	Pos.	+	++	0
3	—	—	—	78	40	51	—	18.8	16.3	19.8	83	52	Pos.	—	0	++	+1
4	—	—	—	190	30	16	—	21.6	17.0	21.6	95	60	Neg.	—	+	0	-1
5	155	268	173	205	44	21	88	—	—	—	90	—	Pos.	—	0	+	+2
6	122	161	132	239	33	14	89	18.7	16.9	25.8	90	52	D. pos.	—	0	0	+2
7	89	89	100	105	33	31	69	18.3	15.1	19.0	95	40	—	—	0	0	+4
8	139	155	83	228	10	4	95	22.1	15.8	22.3	100	50	Neg.	—	0	+	+3
9	450	455	101	461	61	13	97	20.2	15.7	20.5	90	52	D. pos.	—	0	++	+3
10	83	161	194	195	178	96	52	19.8	18.9	24.7	95	77	—	—	0	0	+1
11	305	322	106	250	51	20	81	21.3	16.9	27.5	95	43	Neg.	—	0	+	+2
12	78	95	122	50	22	44	64	—	—	—	100	44	—	—	+	0	-1
13	100	155	155	155	22	14	91	23.7	14.3	19.2	86	42	Pos.	Pos.	0	++	-1
14	272	239	88	300	122	37	58	19.0	16.2	18.7	100	44	Neg.	—	+	++	-1
15	172	94	55	211	144	68	+23	19.5	15.9	19.8	95	50	—	Pos.	+	0	+2
16	245	165	67	255	110	43	36	16.5	13.5	16.6	90	58	—	D. pos.	+	+	0
17	39	50	128	45	17	38	70	16.4	14.7	16.8	83	58	—	Pos.	+	0	0
18	161	217	135	167	17	87	70	18.5	13.6	18.1	83	66	—	Neg.	+	++	+3
19	83	110	132	128	155	43	67	21.7	20.9	23.7	95	—	Neg.	—	0	++	+1
20	44	81	184	55	78	142	23	16.7	20.0	25.5	111	43	Pos.	—	0	—	+2
21	56	95	170	56	0	0	100	16.7	14.8	22.0	100	45	Neg.	—	+	+	+1
22	44	61	138	50	22	44	68	19.6	15.2	20.8	83	42	—	—	+	++	+3
23	39	94	242	317	111	35	86	20.0	15.6	16.1	62	44	Pos.	—	0	++	0
24	83	150	181	95	80	84	54	18.8	16.5	20.0	90	68	—	—	0	++	+2
25	33	22	67	90	40	44	34	20.7	17.5	23.6	125	50	D. pos.	—	0	++	+1
26	70	190	272	415	185	45	83	20.3	15.4	21.9	116	—	Pos.	—	0	++	+3
27	67	61	91	78	17	22	76	21.0	17.0	19.5	80	68	D. pos.	—	0	++	+2
28	56	83	148	222	28	12	92	20.0	14.6	20.7	80	40	—	Pos.	0	++	+3
29	289	445	154	545	330	61	60	20.4	16.0	18.6	86	43	Pos.	—	0	++	+2
30	89	117	131	155	22	14	89	23.2	15.5	20.4	100	40	—	—	0	+	0
31	500	605	121	565	38	7	94	20.9	13.9	19.0	63	30	—	—	0	++	+2
32	378	372	98	33	50	152	+55	—	—	—	74	—	Neg.	Neg.	0	+	+2
33	144	167	116	100	67	42	42	21.0	18.5	21.4	72	46	—	—	0	++	+2
34	189	278	147	44	33	75	49	15.6	15.5	16.1	76	30	—	D. pos.	0	+	0
35	139	122	88	139	61	43	50	—	—	—	64	39	Pos.	—	0	+	+2
36	78	105	135	33	28	85	37	18.0	14.5	17.8	80	47	Neg.	—	+	++	0
37	189	150	80	72	44	61	24	21.7	17.4	22.2	82	28	—	—	+	++	+1
38	17	22	129	55	9	15	88	17.4	16.2	18.4	80	47	Pos.	—	+	++	+1
39	133	183	138	44	22	50	64	17.5	14.7	18.2	66	58	—	—	0	0	+2
40	111	100	90	167	22	13	86	18.8	13.0	18.3	80	38	Neg.	—	0	++	+2

U.A./Cr. ratio: 0 = Unchanged; + = Increased.

* Brought forward from Table I.

and 22 a change of less than 1 g./100 ml. No consistent significant alteration was observed between the haemoglobin levels estimated at maximum hypoglycaemia and 4½ hours later.

As these cases were not under continuous treatment in a metabolic ward, it was considered that any change in the urinary uric-acid/creatinine ratio of less than 40% might be fallacious. Only 11 cases (27.5%) had an increase of more than 40% during the course of treatment. Of these 11 cases, 8 had marked clinical improvement.

Satisfactory total neutral 17-ketosteroid estimations were made in only 8 cases, which is obviously an insufficient number from which to draw conclusions; but it is perhaps of interest that those cases which showed clinical improvement had either a reduction or no change in ketosteroid levels.

The most striking biochemical result of all these investigations was the almost constant decrease in serum potassium levels during hypoglycaemia and an increase in these

Lowering of the fasting blood sugar level, by amounts ranging from 12 to 66% of that level, was achieved in all of the 36 cases examined. Contrary to expectations, little correlation was apparent between the degree of eosinophil depression and either the percentage depression of blood sugar relative to the fasting value or the absolute values for blood sugar obtaining during hypoglycaemia.

A wide variation in susceptibility both to the hypoglycaemic action of insulin and to the eosinopenic action of hypoglycaemia was apparent. In Case 37, for example, a fall in the blood sugar from 82 to 28 mg./100 ml.—a drop of 66%—produced only a 24% reduction in eosinophils whereas in Case 27 a fall in blood sugar from 80 to 68 mg./100 ml. produced an eosinophil depression of 76%.

Of the 36 adequately controlled cases, 34 showed a depression of eosinophils following hypoglycaemia; 26 of these had decreased by 50% and 15 by more than 75% at the 3 p.m. count.

Comparison of the 10 a.m. figures for control and "hypo." days showed that there was no consistent change in eosinophils during hypoglycaemia.

Of the two patients who failed to show any depression of eosinophils, one (Case 32) never had a good hypoglycaemic reaction clinically, although his insulin dosage was raised to 116 units. Nevertheless, on the last day of treatment his eosinophils did in fact fall from 483 at 10 a.m. to 211 at 3 p.m.—a true depression of 55%. Unfortunately, the blood sugar was not estimated. The other patient (Case 15) showed a considerable spontaneous decrease of eosinophils during the control day, a decrease materially unaltered by clinically adequate hypoglycaemic reactions. Case 32 showed only very slight clinical improvement, and Case 15 none whatever.

The Adrenaline Test

The effect upon circulating eosinophils of 0.3 mg. of adrenaline hydrochloride, given subcutaneously in the front of the forearm, was estimated by comparing the change produced after four hours in the number of eosinophils with that occurring spontaneously over a similar period on a previous control day.

The patient remained in bed until the completion of the test. A normal breakfast was given at about 7.30 a.m. and then no food until lunch at 12.30 p.m. Eosinophils were counted at 12 noon and again four hours later, the adrenaline injection being given immediately after the first eosinophil count on the appropriate day. The 4 p.m. figures were expressed as a percentage of the 12 noon value, comparison of these percentages revealing the change produced by adrenaline.

Thirty-nine cases were tested in this way, the results being as follows:

Eosinophil depression	..	>50%	..	30-49%	..	<30%
Men (17 cases)	..	7	..	2	..	8
Women (22 cases)	..	6	..	5	..	11

Thus half of both the male and the female cases showed an insignificant change (leading article, *Lancet*, 1950, 1, 1042), about one-third gave the response stated to be normal by Recant *et al.* (1950), and the remainder showed a distinct but less than normal depression.

Of the 22 patients showing marked clinical improvement, 21 had an adrenaline test performed before therapy was instituted. Of these, 8 showed a positive reaction (eosinophil depression >50%), 9 showed a negative reaction (eosinophil depression <30%), and 4 showed a doubtful positive reaction (eosinophil depression 30-49%). Of the 9 patients showing a slight clinical improvement and the 8 patients showing no change, 4 had a positive reaction, 10 a negative reaction, and 3 a doubtful reaction. The patient who deteriorated had a positive reaction. There does not seem to be a correlation, therefore, between the adrenaline test results and the degree of clinical improvement.

The eosinophil count varies very considerably in the same person from day to day and in the course of the day, and we are well aware that a procedure involving only one control and one test day cannot be highly accurate. It was hoped, however, that this relatively crude test would prove of value in distinguishing those patients who would respond well to therapeutic hypoglycaemia, but it has not done so. Furthermore, no correlation was found between the adrenaline test and any of the laboratory tests carried out.

There is a suggestion that the cases giving a negative adrenaline reaction show a smaller increase in weight and that a smaller proportion of them achieve a satisfactory

depression of eosinophils than occurs in the adrenaline-positive cases, but the test certainly does not decide which patients will respond well to insulin therapy.

A.C.T.H. Test

The effect of A.C.T.H. upon circulating eosinophils was estimated in 10 patients before treatment, the conduct and timing of the test being exactly the same as for the adrenaline test except that a dose of 12.5 mg. A.C.T.H. was injected intramuscularly after the first eosinophil count. This small dose was used partly to stretch our supply to its maximum, but also to ascertain whether any considerable variation in individual susceptibility to the eosinophil-depressing action occurred, and, if so, whether the "sensitive" group would respond better to insulin therapy than the insensitive.

Of the 10 patients tested, 6 showed a depression of 50% or more of circulating eosinophils after four hours (of these, 4 had a marked clinical improvement and 2 showed no clinical change); 2 a depression between 30 and 50% (both these patients showed only slight clinical improvement), and 2 no significant change (one with marked and one with slight clinical improvement). One of the cases with a negative A.C.T.H. reaction and both cases with a doubtful positive had negative adrenaline reactions; the other negative A.C.T.H. case did not, unfortunately, have an adrenaline test. Of the 6 showing positive A.C.T.H. reactions 3 cases had negative, 1 case had a doubtful positive, and 2 cases had a positive adrenaline reaction.

From the above it is obvious that our results show no correlation between the adrenaline and A.C.T.H. reactions or between either of these and the clinical progress of the cases.

Clinical Follow-up of Patients

Of the 40 patients, up to date 25 have been followed up for periods varying from four weeks to four months.

Of those showing marked clinical improvement (16 of the 25), 10 (Cases 1, 13, 14, 18, 19, 23, 24, 25, 27, 29) maintained their improvement for four to six weeks after completion of treatment. The remaining six (Cases 2, 3, 9, 26, 28, 31) relapsed after periods varying from two to five weeks after completion. Of these, Case 2 was given a second course of insulin lasting one week, 13 weeks after the first course, with slight improvement only. In the following week she was given one dose of insulin with little change, and shortly after this she developed gastroenteritis followed by attacks of spontaneous hypoglycaemia, during which time her arthritis again improved. This case will be the subject of a further communication later.

Of those showing slight clinical improvement (5 of the 23), 3 patients (5, 11, 21) maintained their improvement for five weeks, whereas 2 patients (8, 16) relapsed within two weeks of the completion of treatment.

Further clinical follow-ups are proceeding.

Electric Convulsion Therapy

Altogether 11 patients were treated with electric convulsion therapy combined with curare. The technique employed was, after premedication with morphine and atropine, to give 0.5 g. of thiopentone sodium combined with, or followed immediately by, 2 mg. of D-tubocurarine chloride per stone (5.2 kg.) body weight, intravenously. After an interval of 2-2½ minutes an electric shock was given in a dose of 120 or 130 volts for 0.3 second. In 4 patients, as a control, the above technique was used, omitting the actual electric shock in the first instance.

In 2 cases only one shock was given. In one there was no significant change, but in the other there was considerable improvement in the patient's general feeling of well-being and mental outlook, together with reduction of pains in his joints, especially the feet. He could walk without pain and could stand on his toes, a thing he had been unable to do for the past 18 months. This improvement was noted on the evening of the day of therapy and lasted for three weeks, but then his symptoms recurred.

In 2 cases two shocks were given at an interval of five days. In one there was no significant change; the other improved shortly after the first shock, only to relapse again after three days, and after the second shock there was considerable deterioration in the patient's condition in all aspects.

In 1 case three shocks were given at weekly intervals. Considerable improvement was noted on recovery from the shock, and this lasted six days. After the second shock there was again improvement, but much less in degree and lasting only three days. No significant change occurred after the third shock.

In 2 cases two shocks were given at an interval of five days, followed by six more shocks on alternate days over a period of two weeks. One of these cases improved after the first and second shocks, relapse occurring in each instance after 24 hours. After the remaining shocks, however, the patient showed progressive slight improvement of the pains in the joints of the upper limbs, but those in the knees remained unchanged. The improvement noted after completing the course of E.C.T. continued for the next three and a half months, with a slight temporary relapse about six weeks after completion of treatment. The other patient also improved after the first and second shocks, relapsing in each instance after three to four days. Again after the remaining shocks the patient progressively improved, with no relapse, regarding both her general health and the pains and stiffness. This improvement had lasted 10 weeks when she was last seen.

In 3 cases eight shocks were given on alternate days over a period of three weeks following one control. In one patient there was no significant change; in another, slight improvement was seen after the last three shocks, but this was maintained for only two weeks; the third patient progressively improved throughout treatment and continued to do so even more significantly during the next two months, at the end of which time the patient was symptomless and felt extremely well generally, with minimal physical signs.

In 1 case six shocks were given on alternate days over a period of two weeks following one control. Treatment was not continued, because of the development of thrombophlebitis in the arm vein. This patient showed no significant clinical change.

Thus of all the 11 patients treated with E.C.T., 3 showed marked clinical improvement, 3 slight clinical improvement, and 5 no significant clinical change. The average number of shocks given was five.

No significant drop in the number of circulating eosinophils was observed five hours after E.C.T.

Discussion

Arising out of our findings there are a few points worthy of some discussion. Although it was recognized that small doses of insulin had been used for many years for increasing weight, the constancy, magnitude, and rapidity of the increase with the larger doses employed in this series were quite remarkable. This increase was observed even in the worst cases, which had been deteriorating continuously for a year or more in spite of all treatment, including gold, transfusions, etc. Obviously the psychological effect of this weight increase must be considered in the assessment of subjective improvement. In the week after treatment was discontinued about half the cases showed a loss of part of the weight gained. In view of this, fluid balances

were charted for the week before and the week after treatment in the last 14 cases treated. During treatment the hypoglycaemic sweats made any balancing of intake against urinary output quite useless. Even without obvious sweating it was realized that the results might be fallacious, as borne out by Talbott's (1943) observations on a paradoxical increase in weight coupled with diuresis in certain phases of gout, explained by him as due to changes in insensible perspiration. It was thought, however, that even this rough test might give some evidence whether water retention played any part in the very rapid changes in weight.

Before receiving insulin treatment all the patients except one showed a positive fluid balance, whereas after treatment 10 of the cases showed a negative and only 4 a positive fluid balance. Of the 10 showing a negative fluid balance 6 had a loss in weight of 1-3 lb. (0.45-1.36 kg.), 3 had a gain in weight of 1 lb., and in one the weight did not change in the week following treatment (Table III). Observations on fluid balance are continuing.

TABLE III.—Fluid Balance Chart

No.	Pre-Insulin (fl. oz.)			Post-Insulin (fl. oz.)			Gain Wt. (lb.) During Treatment	Change Wt. (lb.) After Treatment	Clinical Progress
	*Intake	Output	Diff.	*Intake	Output	Diff.			
27	59.6	55.8	+3.8	67.1	66.1	+1.0	+7	-1	++
28	66.2	57.2	+9.0	70.8	76.8	-6.0	+9	-1	++
29	44.8	42.0	+2.8	50.9	57.5	-6.6	+11	-1	++
30	52.4	55.4	-3.0	56.0	56.4	-0.4	+9	+1	++
31	58.4	52.0	+6.4	70.3	72.0	-1.7	+9	-1	++
32	65.0	61.7	+3.3	54.0	55.4	-1.4	+6	-2	++
33	59.0	46.4	+12.6	62.0	62.3	-0.3	+6	0	++
34	53.8	22.0	+31.8	56.3	42.0	+14.3	+5	-1	++
35	56.4	50.0	+6.4	64.6	75.1	-10.5	+13	-3	++
36	48.4	42.8	+5.6	45.0	43.3	+1.7	+6	+1	++
37	44.4	41.6	+2.8	50.3	51.4	-1.1	+7	+1	++
38	44.0	40.2	+3.8	44.2	47.3	-3.1	+7	-1	++
39	41.8	38.8	+3.0	55.7	53.7	+2.0	+7	-1	0
40	45.7	45.0	+0.7	45.4	48.8	-3.4	+7	+1	++

One fluid ounce = 28.4 ml. One pound = 0.37 kg. * Average daily figure.

In spite of the high percentage of cases that showed marked clinical improvement, usually starting in the first week, there were no consistent changes in the E.S.R. during the period of observation. This is not in conformity with the findings of Godlowski (1949) in his single case.

The uric acid excretion was significantly increased in only 11 cases, but this is not surprising in view of the comparatively small average increase in uric acid found by Sprague *et al.* (1950) even on administration of 200 mg. of cortisone.

The changes in the serum potassium were the most constant of all the biochemical findings in our series. The reduction of potassium at the height of hypoglycaemia is well recognized (Cantarow and Trumper, 1945), but the rise 4½ hours later, at the point of eosinopenia, is worthy of notice. Sprague found that a drop in potassium was the most constant biochemical finding of any in treatment with cortisone or A.C.T.H.

The absence of correlation of eosinopenia with clinical progress is of interest, as is the constancy of the fall of eosinophils with insulin but absence of change with E.C.T. The suggestion that insulin hypoglycaemia acts by stimulation of the pituitary through the production of adrenaline is borne out neither by the response of the patients to adrenaline—which showed little correlation with their response to insulin—nor by our previous indifferent results when 5 cases of rheumatoid arthritis were treated with adrenaline in oil (unpublished). It seems, however, that direct stimulation of the adrenal cortex, as has been shown to occur in hypophysectomized animals, is more likely;

or the synergic action of insulin and endogenous cortisone may be a factor in our results (Henderson *et al.*, 1950).

It is stressed that the use of insulin hypoglycaemia should not be looked upon, at all events at present, as a new treatment for rheumatoid arthritis. This is only a report on a pilot series of cases, which require further control and follow-up. Further information is being sought on such problems as potassium excretion, fluid retention, correlation of results with A.C.T.H.-sensitivity, and the value of intermittent treatment.

Summary

Forty cases of active rheumatoid arthritis have been treated five times weekly for either three or four weeks with insulin hypoglycaemia.

Twenty-two of these cases showed marked clinical improvement, nine slight improvement, eight no change, and one deteriorated.

Ten maintained their marked improvement and three moderate improvement six weeks after completion of treatment.

In cases showing definite improvement, this usually began within a week of starting treatment.

All cases increased in weight, some remarkably.

The serum potassium was lowered in 34 out of 36 cases at the height of hypoglycaemia, and had risen again in all cases four and a half hours later, at the time of maximal eosinopenia—in 13 significantly above the control value.

Urinary uric acid excretion was significantly raised in 11 cases during treatment, but there was no increase in the neutral 17-ketosteroids in the eight cases in which these were estimated.

The sedimentation rate was not significantly changed.

Fourteen cases showed an increase and three a decrease of more than 1 g./100 ml. in haemoglobin.

Thirty-four cases showed a significant fall in circulating eosinophils four and a half hours after maximal hypoglycaemia. There was no marked correlation, however, between the degree of fall and the degree of hypoglycaemia or the clinical improvement. There was very little correlation between the eosinophil depression produced by adrenaline or A.C.T.H. and either the clinical response or the degree of eosinopenia following hypoglycaemia.

Eleven cases were treated by E.C.T. with an average of five shocks each. Three showed marked improvement, three slight improvement, and five no change.

No significant fall of eosinophils was found as the result of electric convulsion therapy.

We would like to thank Dr. Tyndall, of Messrs. Organon, Ltd., and the Medical Research Council for donations of A.C.T.H., the Empire Rheumatism Council for financial assistance in laboratory expenses, and Drs. J. B. Bennett, T. Northover, R. Pearson, L. Scott White, and J. Thoresby for their help and suggestions; also the nursing and secretarial staff of the unit.

REFERENCES

- Callow, N. H., *et al.* (1938). *Biochem. J.*, **32**, 1312.
 Cannon, W. B., *et al.* (1924). *Amer. J. Physiol.*, **69**, 46.
 Cantarow, A., and Trumper, M. (1945). *Clinical Biochemistry*, 3rd ed. Saunders, Philadelphia.
 Copeman, W. S. C. (1931). *British Medical Journal*, **2**, 1130.
 Godlowski, Z. Z. (1947). *Edinb. med. J.*, **54**, 239.
 — (1949). *Ann. rheum. Dis.*, **8**, 285.
 Henderson, E., *et al.* (1950). *J. clin. Endocrinol.*, **10**, 800.
 Kersley, G. D., *et al.* (1950). *Lancet*, **1**, 703, 1153.
 King, E. J. (1946). *Micro-analysis in Medical Biochemistry*, 1st ed. Churchill, London.
 Langecker, H. (1928). *Arch. exp. Path. Pharm.*, **134**, 155.
 Miller, R. A., *et al.* (1941). *Proc. Soc. exp. Biol., N.Y.*, **47**, 449.
 Rando'ph, T. G. (1949). *J. Lab. clin. Med.*, **34**, 1696.
 Recant, L., *et al.* (1950). *J. clin. Endocrinol.*, **10**, 187.
 Sargant, W., and Slater, E. (1948). *An Introduction to Physical Methods in Psychiatry*, 2nd ed. Livingstone, Edinburgh.
 Sprague, R. G., *et al.* (1950). *Arch. intern. Med.*, **85**, 199.
 Talbott, J. H. (1943). *Gout*. Oxford Univ. Press, London.

THE EFFECT OF CORTISONE ON THE CARDIOGRAM IN CHRONIC ADRENAL INSUFFICIENCY*

BY

WALTER SOMERVILLE, M.D., M.R.C.P.

Senior Registrar, Cardiographic Department, Middlesex Hospital; formerly Assistant in Medicine, Peter Bent Brigham Hospital, Boston, U.S.A.

The beneficial effects of cortisone (17-hydroxy-11-dehydrocorticosterone) on chronic adrenal insufficiency (Thorn, Bayles, Massell, Forsham, Hill, Smith, and Warren, 1949) suggested that the cardiovascular system, which is often involved in this condition, might take part in the improvement. In a typical and severe case the heart is smaller than normal, the blood pressure lower, and the cardiogram shows non-specific abnormalities. These are, in order of frequency, abnormally flat or inverted T waves, prolonged QT interval, low voltage, prolonged PR or QRS interval, and depressed ST segment. On the other hand, the cardiovascular system, including the cardiogram, may be normal (Somerville and Levine, 1950).

Present Series

This series comprises 11 patients (3 males and 8 females) with proved chronic adrenal insufficiency treated with cortisone under the direction of Dr. George W. Thorn. The ages ranged between 14 and 55 years. All had been treated previously with replacement therapy for periods of 2–28 years (average 9 years). The cardiograms of six patients showed one or more of the abnormalities mentioned above. In five instances the cardiograms were normal. The clinical and metabolic changes following cortisone therapy in these patients have been reported elsewhere (Thorn, Forsham, Bennett, Roche, Reiss, Slessor, Flink, and Somerville, 1949).

Cortisone was given by intramuscular injection in total doses of 163 to 850 mg. over periods of 5 to 18 days. In three instances cortisone pellets were implanted subcutaneously and the dosage was estimated from the predetermined rate of absorption of the pellets. Several of

Table showing changes Occurring in the Cardiogram during Cortisone Therapy

Case No.	Cortisone			Cardiogram					Result
	Dose (mg.)	Period of Admin. (Days)		Low Voltage	Prolonged PR	QT	De-pressed ST	Ab-normal T	
1	800	18	Before After					++	Improved
9	300	27	Before After					+	"
22	163	36	Before After	+	+			++	"
28	533	19	Before After	+		+		++	"
6	290	17	Before After	+		+	+	++	Unchanged
5	530	20	Before After	See note				++	"
12	375	9	Before After	+				++	
15	276	9		Normal before and after					
49	275	4		"	"	"	"	"	
63a	850	5		"	"	"	"	"	
71	200	5		"	"	"	"	"	

Note.—Abnormalities persisting after cortisone may have been, in part, residue of recent pericarditis.

* From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston, U.S.A.