Current views on the pathological processes involved are presented and the value of electrodiagnostic tests is discussed.

No clear evidence emerges from this series to prove the value of facial-nerve decompression, and there is a strong case for a large-scale clinical investigation to evaluate this and other methods of treatment.

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REFERENCES

- Aitken, R. S., and Brain, R. T. (1933). *Lancet*, 1, 19.
 Ballance, C., and Duel, A. B. (1932). *Arch. Otolaryng. (Chicago)*, 15, 1.
 Bell, C. (1821). *Phil. Trans.*, 111, 398.
 Blunt, M. J. (1956). *J. Laryng.*, 70, 701.
 Cawthorne, T. (1946). *Laryngoscope (St. Louis)*, 56, 653.
 — (1951). *Proc. roy. Soc. Med.*, 44, 565.
 — (1952). *Lancet*, 2, 39.
 Collier, J. (1951). *Proc. roy. Soc. Med.*, 44, 569.
 — (1954). In *Modern Trends in Diseases of the Ear, Nose, and Throat*, edited by M. Ellis, p. 202. Butterworth, London.
 Denny-Brown, D., Adams, R. D., and Fitzgerald, P. J. (1944). *Arch. Neurol. Psychiat. (Chicago)*, 51, 216.
 Findlay, J. P. (1950). *Facial Paralysis*. Angus and Robertson, Sydney.
 — Guldberg-Møller, J., Olsen, S., and Kettel, K. (1959). *A.M.A. Arch. Otolaryng.*, 69, 220.
 Hallpike, C. S. (1935). *Proc. roy. Soc. Med.*, 28, 226.
 Hunt, J. R. (1907). *J. nerv. ment. Dis.*, 34, 73.
 James, J. A., and Russell, W. R. (1951). *Lancet*, 2, 519.
 Jefferson, G., and Smalley, A. A. (1938). *J. Laryng.*, 53, 417.
 Kettel, K. (1947). *Arch. Otolaryng. (Chicago)*, 46, 427.
 — (1959). *Peripheral Facial Palsy*. Blackwell, Oxford.
 Korkis, F. B. (1959). *A.M.A. Arch. Otolaryng.*, 70, 562.
 Krarup, B. (1958). *Acta oto-laryng. (Stockh.)*, Suppl. 140, p. 201.
 Mackenzie, I. C. K. (1955). *Lancet*, 1, 377.
 Morris, W. M. (1938). *Ibid.*, 1, 429.
 Schirmer, O. (1903). *Albrecht v. Graefes Arch. Ophthal.*, 56, 197.
 Sullivan, J. A. (1952). *Laryngoscope (St. Louis)*, 62, 449.
 — and McAskill, K. (1952). In *Diseases of the Ear, Nose, and Throat*, edited by W. G. Scott-Brown, 2, 221. Butterworth, London.
 Tumarkin, I. A. (1936). *Proc. roy. Soc. Med.*, 29, 1685.
 — (1951). *Ibid.*, 44, 572.
 Wyburn-Mason, R. (1954). *Brit. med. J.*, 2, 679.

A NEW TREATMENT OF ANOREXIA NERVOSA

BY

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Ever since Gull (1874) first described anorexia nervosa it has continued to present difficulties to general physicians and psychiatrists alike. A great deal has been written about the condition, many detailed psychiatric and endocrinological studies have been made, but little advance in treatment has occurred. Early on, Gull recognized that the patient's refusal to eat was due to "a morbid mental state" and "the inclinations of the patient must be in no way consulted . . . patients should be fed at regular intervals and surrounded by persons who would have moral control over them; relatives and friends being generally the worst attendants." He thought the prognosis was on the whole a favourable one, but doctors have since found these patients very unwilling to eat despite all the "moral" and other kinds

of persuasion given. In recent years frank pessimism has sometimes been expressed about the eventual outcome of treatment. A recent study from the Maudsley Hospital showed that 15% of patients in the group followed up had died from the illness or its complications.

Hormone preparations, including thyroid, insulin, and cortisone, have all been tried with little effect. Electric shock has frequently been given, but the results are far from encouraging, and more harm than good may be done unless there is marked endogenous depression. Because of the unsuccessful results of treatment in so many patients, one of us (Sargent, 1951) treated selected chronic cases by modified leucotomy, and suggested that this was preferable to the much graver risks of allowing states of inanition to continue indefinitely. Since then the fashion in treatment has returned almost to where it started. In Gull's time, tube feeding was sometimes used as a last resort, but most workers since then have agreed that it is most undesirable from a psychological point of view. Yet within the last two years papers have again been published advocating a routine use of tube feeding as the most practical and best alternative to modified leucotomy (Williams, 1958; Wall, 1959).

In a letter on the general undesirability of tube feeding in this disease, we mentioned the use of a new method of treatment in which modified insulin treatment was combined with large doses of chlorpromazine (Dally, Oppenheim, and Sargent, 1958). We have found this method to be far more effective and simple than any other we have tried. For many years we used modified insulin alone in the treatment of anorexia nervosa, but with very little success. Then N. Moore, in a personal communication to one of us (W.S.), said that, while investigating the use of reserpine in schizophrenia at St. Patrick's Hospital, Dublin, he had also noted its value in the treatment of certain cases of anorexia nervosa. The use of reserpine, however, produced states of severe depression in some of our patients, and this led us to try chlorpromazine instead. Then we started to combine chlorpromazine with the modified insulin treatment. This paper now reports the first 20 cases of anorexia nervosa treated by this combined method over the past three years, and compares results with those obtained in 24 similar cases, all referred for a psychiatric opinion, and treated in St. Thomas's Hospital by other methods over the past 20 years. Table I compares these two groups of patients.

TABLE I.—A Comparison of Patients of Groups A (Chlorpromazine and Insulin) and B (Other Methods)

	Group A	Group B
Average age at onset of illness	18.8 ± 5.5 years	18.0 ± 5.2 years
.. weight lost before treatment	37.1 ± 15.1 lb.	33.5 ± 10.3 lb.
.. length of illness before treatment at S.T.H.	49 ± 71 months	22 ± 18 months

Selection of Patients

Anorexia nervosa is a syndrome which needs to be clearly defined. We regard the essential criteria for its diagnosis to be: (1) refusal to eat, whether or not accompanied by anorexia at the start; (2) severe loss of weight; (3) absence of evidence of schizophrenia, severe depression, or organic disease; and (4) amenorrhoea of at least three months' duration in female patients. Eventually most cases of anorexia nervosa will also develop

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obstinate constipation, hypotension, bradycardia, acrocyanosis, and a new growth of downy hair on the limbs and trunk, and in many patients physical overactivity becomes marked despite extreme emaciation. One or more of these secondary signs and symptoms were present in all 44 patients. Some writers regard amenorrhoea as an essential part of a syndrome which excludes male patients by definition. Like Gull, however, we believe that male patients can be affected, though uncommonly, and one very typical male patient is included in our group of 20.

Method Used

Patients are put to bed at the start of treatment and told they must stay there until they regain near normal weight (depending on the previous weight, age, height, etc.). Thus food intake can be supervised, and risks of using large doses of these drugs in debilitated patients are minimized. Chlorpromazine is given by mouth, starting with 150 mg. a day and increasing by 75 mg. a day to the limit of the patient's tolerance. As much as 1,000 mg. a day has been needed in difficult patients, one of whom weighed only 72 lb. (32.7 kg.). If signs of Parkinsonism increase, small doses of benzhexol hydrochloride can also be added. Modified insulin therapy is also begun at once, starting with 5 units and progressively increasing the dose until the patient sweats and becomes drowsy. Then interruption takes place with a large meal. Precautions are also taken throughout the day to avoid occurrence of late hypoglycaemia. None of our patients reacted with abnormal sensitivity, though this has been thought by some to be a theoretical objection to the use of insulin in anorexia nervosa. The average morning dose in the series was 60 units, varying from 40 to 80 units according to individual sensitivity.

At first a light diet is given. It includes frequent fortified milk drinks and is steadily increased from 1,500 calories to 4,000 calories a day. In this way abdominal discomfort, a common cause of complaint in the early stages of treatment, is reduced to a minimum. The patient's confidence is gained, and reassurance is constantly given, but no attempt is made to uncover psychological problems or to deal with them until the weight is nearly normal. Then the drugs are reduced and the patient is allowed up. A week later, provided she is still eating satisfactorily, she is discharged home. Attempts are made to follow up patients for at least a year, and supportive psychotherapy with the patient in a remission seems valuable in preventing relapse. A maintenance dose of chlorpromazine may also help to prevent relapse in some patients.

Results

In order to simplify the reporting of our results, readmissions have been regarded as fresh cases. Three of our 20 patients treated by combined chlorpromazine and insulin (now termed group A) had to be readmitted once, and

TABLE II.—Results of Treatment

	No.	Average Wt Gain (lb./Week)	Average Stay in Hospital
Group A	25	4.4 ± 1.3	34.9 ± 12.2 days
B	28	1.3 ± 1.6	58.4 ± 6.4 "
Williams (1958) (patients intubated)	8	2.8	67.6 days
Stafford-Clark (1958) (mainly psychotherapy) .. .	19	1.9	150 days (approx.)

only one twice. Four of the 24 patients treated by other methods and by other physicians at the hospital (now termed group B) were readmitted once.

It will be seen from Table II that the patients in group A gained an average of no less than 4.4 lb. (2 kg.) a week, and their average stay in hospital was only 34.9 days. This compares with the patients of group B, who gained an average of only 1.3 lb. (0.58 kg.) a week during an average stay of 58.4 days. The difference between these results is highly significant ($p > 0.01$). Individual details of our group A patients are given in Table III.

In the past, a weight gain of 2 lb. (0.9 kg.) a week or more has been regarded as a very satisfactory result (Ormerod, 1910). Williams (1958), reporting a series of cases treated at the London Hospital, concluded that only tube feeding produced satisfactory results, but eight such cases of his gained only an average of 2.8 lb. (1.27 kg.) during an average of 67.6 days. Stafford-Clark (1958) has also reported a group treated mainly

FIG. 1.—Treatment and resultant change in weight in girl with anorexia nervosa.

TABLE III

Case No.	Sex	Age of Onset	Weight Loss		Months of Illness	Previous Admissions	Weight Gain		Days of Treatment
			lb.	kg.			lb.	kg.	
1	M	12	24	10.9	24	0	24	10.9	38
2	(readmission)	11	N.K.		240	4	32	14.5	25
3	F	21	28	12.7	240	2	11	5.0	63
4	F	16	21	9.5	126	4	21	9.5	21
*5	F	18	24	10.9	16	0	12	5.4	46
6	(readmission)	15	34	15.4	13	0	15	6.8	33
							30	13.6	29
7	F	15	30	13.6	9	0	12	5.4	47
8	F	17	26	11.8	48	0	15	6.8	16
9	F	27	N.K.		72	4	20	9.1	31
							4	1.8	35
						(transferred due to closure of ward)			
10	F	18	28	12.7	24	0	15	6.8	16
11	F	16	29	13.2	3	0	28	12.7	24
12	F	14	38	17.2	9	1	20	9.1	46
13	F	17	30	13.6	6	0	24	10.9	29
*14	(readmission)	14	48	21.8	5	0	36	16.3	26
							11	5.0	35
*15	F	15	80	36.3	15	1	37	16.8	21
16	(readmission)	21	45	20.4	24	0	28	12.7	39
							14	6.4	40
*17	F	20	47	21.3	17	1	34	15.4	27
18	F	20	N.K.		36	3	29	13.2	40
19	F	33	N.K.		36	1	17	7.7	62
*20	F	28	46	20.9	18	0	47	21.3	28
									55

* Treated in a general medical ward.

TABLE IV.—Follow-up Results

	Group A	Group B
Good recovery (menstruation and weight satisfactory)	11	13
Fair recovery (condition stable, but underweight and absent periods)	3	6
No recovery or frequent relapses	3	3
Dead	0	2
Discharged within the last three months and not therefore assessed	3	—
Total	20	24

by psychotherapy who gained an average of only 1.9 lb. (0.8 kg.) over nearly 150 days.

The results of the follow-up are shown in Table IV.

Discussion of Results

Most patients begin to gain weight almost at once when treated with the combination of chlorpromazine and insulin. An example is shown in Fig. 1. This girl was treated for 40 days with insulin before meals, during which time she gained only 3 lb. (1.4 kg.). She was then given chlorpromazine and modified insulin, and her weight rose rapidly. Fig. 2 shows a patient whose "belly touched her backbone" on admission; she was depressed, untruthful, and resisted all attempts to make her eat. After five weeks' treatment she became cheerful, co-operative, and almost normal again after a gain in weight of 20 lb. (9 kg.).

Some of the large initial weight increase is undoubtedly due to water retention, but we regard this as a favourable sign, and it is usually accompanied by increasing cheerfulness and more ready acceptance of treatment. The underlying worry about eating often persists, but no longer frightens the patient to the point of self-starvation. It seems to be the combination of insulin and chlorpromazine that is so effective, for neither drug given alone, nor given with an insufficient dosage of the other, produces as good results. What is more, if either the chlorpromazine or the insulin is stopped before the weight is satisfactory, or if the patient is allowed up and about too soon, she is likely to relapse. Putting the

patient back to bed and replacing either drug in proper amounts will quickly reverse this tendency.

With the patient totally confined to bed and given very careful nursing, no complications have so far been encountered. But late hypoglycaemia can occur if the patient is left too long unobserved, and the hypotensive effects of chlorpromazine in such large doses in emaciated persons can be severe if the patient is allowed up too early. A good ward sister who is firm but kindly, and sees that all food given is really eaten, contributes to the success of the method, and the doctor may still at times need to apply "moral" pressure as in Gull's day. The treatment tends to fail if any one part of it is omitted or is given too much emphasis at the expense of another. However, in order to dispel any idea that our results were due solely to a well-staffed and specialized ward (though this can be very helpful), we must mention that 5 of our 20 patients have also been treated in the general medical wards of St. Thomas's Hospital. These five are marked in Table III, and have obviously done just as well as those treated in our own psychiatric beds.

Follow-up of treated patients for at least a year or more after apparent recovery appears to be desirable. The view that all is well once the periods have returned is not always correct, and some of our patients have relapsed even after the return of regular menstruation. But in general we are much more satisfied with our results and follow-up findings since using this particular method of treatment, though we realize that much more time will be needed to assess its full and lasting effects on the natural course of the illness.

Summary

A new method of treatment of anorexia nervosa is described which combines the use of large doses of chlorpromazine with modified insulin treatment carried to the point of sweating and drowsiness. The patient is also confined totally to bed until the weight is nearly back to normal. The treatment of 20 patients by this method is reported, and results are compared with those obtained in 24 similar patients treated in St. Thomas's Hospital by other methods and with published results from other hospitals. It has been found more effective than any other form of treatment used previously.

REFERENCES

- Dally, P. J., Oppenheim, G. B., and Sargent, W. (1958). *Brit. med. J.*, 2, 633.
Gull, W. W. (1874). *Trans. clin. Soc. Lond.*, 7, 22.

FIG. 2.—Photographs of patient before and after treatment.

- Ormerod, J. A. (1910). In *A System of Medicine*, edited by C. Allbutt and H. D. Rolleston, vol. 8. Macmillan, London.
- Sargant, W. (1951). *Lancet*, 2, 87.
- Stafford-Clark, D. (1958). *Brit. med. J.*, 2, 446.
- Wail, J. H. (1959). *Amer. J. Psychiat.*, 115, 997.
- Williams, E. (1958). *Brit. med. J.*, 2, 190.

CLINICAL EVALUATION OF BENZTHIAZIDE, AN ORAL DIURETIC

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The synthesis of chlorothiazide has stimulated the search for other substitution derivatives of the benzothiadiazine nucleus in the hope that these newer compounds might be less prone to induce potassium depletion. The newest compound belonging to this group is benzthiazide (3-benzylthiomethyl-6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide) (Fig. 1). The mode of action of chlorothiazide has been studied extensively (Bayliss *et al.*, 1958; Matheson and Morgan, 1958; Watson *et al.*, 1958), and a direct comparison with this drug provides the most satisfactory method of assessing the value of a new compound of this type.

FIG. 1.—Structural formulae of principal benzothiadiazine derivatives.

Material and Methods

The action of benzthiazide as compared with that of chlorothiazide was studied in two young men admitted to hospital for the investigation of minute tuberculous foci; they had never been oedematous, and in all other respects their health was normal. The subjects continued moderate activity and no drugs other than those on trial were administered. Though dietary electrolytes were not accurately standardized, food and fluid intakes on the days of the experiments were quantitatively and qualitatively similar, and on this regime the two men had a similar pattern of electrolyte excretion. Urine was collected by evacuating the bladder at two-hourly intervals for 10 hours, and then a pooled collection was made of the urine passed in the next 14 hours. Observations were made both before and after the administration of single doses of 100 mg. of benzthiazide or 1 g. of chlorothiazide, at least three days being allowed to elapse before another experiment with a diuretic was made. The two-hourly specimens

were collected with strict anaerobic precautions, but mineral oil was not used, as it has been observed that CO₂ is soluble in paraffin (Gambino, 1959). Without delay the pH, CO₂-content, and titratable acidity of these samples were determined; the volume and content of sodium, potassium, and chloride of all specimens were measured.

A clinical trial was conducted on 15 in-patients with oedema. The cause of the oedema was congestive cardiac failure in nine patients and hepatic cirrhosis in the remaining six. Fluid consumption was maintained at 1.5 litres daily and sodium intake was restricted to 25 mEq a day (1.5 g. NaCl diet). With the exception of one patient (Case 10) no potassium supplements were given. All the patients were weighed daily and 24-hour collections of urine were made throughout. The trial was introduced by a four-day control period of bed rest, but this was curtailed in a few patients because of the severity of their condition; if treatment other than diuretics was being given prior to the trial this was kept constant throughout. After the control period one of the diuretics under trial was administered for four days; an interval of two to four days without a diuretic was then allowed before administering the other drug for a further four days. The drug chosen to initiate therapy was alternated in successive patients. Daily dosage totalled 1 g. of chlorothiazide or 100 mg. of benzthiazide. Urine volume and electrolyte excretion were measured daily, and the serum electrolytes and blood urea were estimated twice weekly. Screening tests for blood dyscrasia and hepatic dysfunction were also carried out.

Technical Methods.—Sodium and potassium were estimated by flame photometry; chlorides by potentiometric titration, using a silver electrode; and carbon dioxide by a manometric method. Titratable acidity was determined by titration with N/50 NaOH, using bromthymol blue indicator; urine pH by a glass electrode pH meter; and urine bicarbonate from the carbonic acid-bicarbonate curve according to pH (Peters and Van Slyke, 1932).

Comparison of Action in Normal Subjects

Urine changes in the two men were similar, and the results have therefore been presented as a mean (Table I, Fig. 2).

TABLE I.—Total 10-Hour Urinary Excretion After Benzthiazide and Chlorothiazide in Two Normal Men

	Control	Benzthiazide (100 mg.)	Chlorothiazide (1 g.)
Potassium (mEq)	43	74	63
Sodium "	51	139	144
Chloride "	76	176	142
Bicarbonate "	7.8	7.7	36.8
Titratable acid "	8.3	9.9	4.7
Water (ml.)	1,170	1,840	2,080

Urine Volume.—After both drugs the urine flow was maximal in the first six hours and had returned to little above control values within 10 hours, though peak water excretion was slightly delayed after benzthiazide as compared with chlorothiazide.

Electrolyte Excretion.—This ran parallel to water excretion after both drugs. Sodium excretion was similar, but benzthiazide caused a greater loss of chloride.

Changes in Acidity.—Titratable acid and pH were little altered by benzthiazide; chlorothiazide led to the secretion of an alkaline urine during the first six hours,