PAPERS AND ORIGINALS

Chronic Granulocytic Leukaemia: Effect of Elective Splenectomy on the Course of Disease

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British Medical Journal, 1975, 1, 175-179

Summary

Conventional treatment by drugs or irradiation produces little prolongation of life in patients with chronic granulocytic leukaemia (C.G.L.) because the onset of metamorphosis of the disease from a chronic to an acute or subacute leukaemic process is not substantially postponed. Isolated clinical observations as well as both cytogenetic and cytokinetic evidence suggest that the spleen may play a special though not exclusive role in the development of undifferentiated cell clones which lead to metamorphosis of C.G.L. The results of a study of elective splenectomy during the chronic phase of the disease are reported. Twenty-six patients with C.G.L. underwent splenectomy during clinical remission of their disease, and there were no deaths after the operation. Twenty-one patients were alive at the time of writing, two of them eight years after splenectomy. Five cases of metamorphosis of C.G.L. to a refractory phase occurred whereas 10 would have been expected, a significant

difference. After the onset of metamorphosis the quality of life was better in splenectomized than in non-splenectomized patients. These results show that splenectomy is a reasonable and safe procedure in C.G.L., and its apparently beneficial effects on prognosis justify a larger controlled clinical trial.

Introduction

Despite important advances in the management of the acute leukaemias there has been little significant progress in the treatment of chronic granulocytic leukaemia (C.G.L.) (Galton and Spiers, 1971). Fifty years ago the median survival from diagnosis of untreated patients with C.G.L. was 19 months (Minot *et al.*, 1924). In a Medical Research Council study in 1968 the median survival of patients who received splenic irradiation was 28 months while patients treated with busulphan fared better at 39.5 months (Medical Research Council, 1968). A retrospective comparison of radiotherapy and busulphan (Monfardini *et al.*, 1973) and a study of C.G.L. treated with dibromannitol (Dibromannitol Study Group, 1973) showed similar results. Though current therapy for C.G.L. improves the quality of life it seems to add only about 20 months to its duration. Despite its small effect upon survival busulphan therapy remains popular because of its convenience and good short-term results; this has retarded research into other forms of treatment for C.G.L. (Galton and Spiers, 1971).

In the Medical Research Council's study over 70% of the patients died with uncontrolled leukaemia. Their disease had undergone metamorphosis (Baikie, 1966, 1969) to a more refractory neoplasm in which the features of C.G.L. in its chronic phase were partly or wholly lost. Despite some recent improvement (Spiers *et al.*, 1974) treatment is still not strikingly effective once metamorphosis has occurred and measures aimed at postponing the onset of this change and prolonging the chronic phase of C.G.L. may be the most promising way of improving survival in this disease. We have previously suggested (Baikie, 1968; Galton and Spiers, 1971; Spiers, 1973) that elective splenectomy early in the course of C.G.L. might prolong survival by deferring metamorphosis. Patients with C.G.L. who have enjoyed especially long survival seem to include an undue

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proportion with relatively slight splenomegaly before treatment or prolonged regression of splenic enlargement after treatment. A few patients with C.G.L. who underwent splenectomy for a variety of reasons have had haematological remissions without chemotherapy (Cutting, 1967) or unusually long survivals (Dubois-Ferriere and Rudler, 1967; Meeker *et al.*, 1967). The spleen in C.G.L. is known to contain Philadelphia (Ph¹)-positive cells before metamorphosis has occurred and Ph¹-positive cells with additional chromosomal changes after metamorphosis (Spiers and Baikie, 1965; 1968). The proliferative activity of immature granulocytic cells in the spleen differs from that observed in the bone marrow (Brandt, 1969; Galbraith, 1969), and recent cytogenetic observations suggest that the spleen may sometimes have a primary role in the development of aneuploid clones of leukaemia cells which lead to metamorphosis of C.G.L. (Hossfeld and Schmidt, 1973; Mitelman, *et al.*, 1974). Pharmacodynamic or, possibly, immunological factors may make the spleen a particularly suitable site for the emergence of aberrant clones, and if so its removal could be expected to postpone metamorphosis though it might not prevent it. The beneficial effects of prior splenectomy certainly extend beyond the time when metamorphosis has actually occurred. Refractory splenomegaly with pain, anaemia, a high transfusion requirement, and thrombocytopenia which is not corrected by platelet transfusion are commonly encountered in the terminal phase of C.G.L. The absence of these complications improves the quality of life and probably also its duration even though the C.G.L. is no longer chronic (Schwarzenberg *et al.*, 1973; Spiers *et al.*, 1973). Some of these considerations were felt to justify a pilot study of elective splenectomy in C.G.L., and we now report the results nine years from its inception.

Patients and Methods

The patients were under our personal care at various hospitals at the time of splenectomy and had typical clinical and haematological features of C.G.L. (table I) with raised peripheral blood leucocyte counts and blood films showing a complete spectrum of granulocytic cells. The Ph¹ chromosome was identified in bone marrow or spleen preparations or both in every case. Bone marrow was aspirated in all cases and no patient had obvious myelofibrosis. In no case was splenectomy preceded by iatrogenic marrow hypoplasia attributable to busulphan or other treatment. Of the 26 patients 15 were men and 11 women; their

ages ranged from 16 to 64 years. Neutrophil alkaline phosphatase scores were recorded in 23 cases; 18 were below while five were within the normal range. Most of the patients were treated initially with busulphan (table I).

The criteria for acceptance into this study were (a) an unequivocal diagnosis of C.G.L. still in its chronic phase; (b) a satisfactory clinical and haematological response to initial treatment for C.G.L.; (c) age under 65 years and the absence of other illness making for a poor surgical risk; and (d) willingness to undergo splenectomy. No other exclusions were made and in particular the persistence of mild to moderate splenomegaly in the presence of a normal blood count did not preclude or postpone operation. We attempted to reduce the platelet count to less than $200 \times 10^9/l$ ($200,000/mm^3$) before surgery and in the busulphan-treated patients this was generally successful. No patient was in fact excluded under provision (b)—that is, unsatisfactory response to busulphan was not observed.

The patients were nursed preoperatively in general medical wards and after operation in general surgical wards. They were not neutropenic and no special isolation measures were adopted. Most of the splenectomies were performed via an upper left paramedian incision confined to the abdomen. Some of the more recent operations were performed with intermittent calf compression before and after the operation (Hills *et al.*, 1972) and the use of ¹²⁵I-fibrinogen for the detection of postoperative venous thrombosis (Jeyasingh *et al.*, 1972). Postoperative anticoagulants were not routinely used.

The follow-up and, in 24 cases, the medical care of these patients after splenectomy remained in our hands, and their principal antileukaemic treatment was busulphan in conventional dosage (table I).

Results

Surgical Experience.—Most of the operations were simple. Massive splenomegaly with dense adhesions such as may be found when splenectomy is performed late in the course of C.G.L. was not seen. There were no operative or postoperative deaths and significant complications occurred in only three patients. One patient (case 9) aged 62 had deep venous thrombosis, and he developed a pulmonary embolus 19 days after the operation. A 39-year-old patient (case 23) developed left pleural effusion, peritonitis, and paralytic ileus. Another patient (case 26) produced a sterile serous discharge from his wound and the

TABLE I—Clinical Details of 26 Patients with Chronic Granulocytic Leukaemia undergoing Elective Splenectomy

Case No.	Age at Diagnosis (Years)	Sex	Haematological Findings at Diagnosis				Treatment before Splenectomy	Treatment after Splenectomy
			Hb (g/dl)	Platelets ($\times 10^9/l$)	W.B.C. ($\times 10^9/l$)	N.A.P. Score* (u)		
1	37	M.	10.3	444	511	1	BUS	BUS
2	29	M.	10.5	475	276	3	SXRT	BUS
3	30	F.	9.4	750	315	5	BUS	Cyclic
4	42	M.	12.3		150		None	BUS
5	27	F.	9.1	800	350		SXRT, BUS	BUS, 6MP, DBM
6	26	M.	10.5	320	160		BUS	BUS
7	64	F.	10.3	485	131	43	BUS	BUS
8	37	F.	7.2	571	520	0	BUS	BUS
9	62	M.	10.6	470	90	27	BUS, HU	Cyclic
10	22	M.	7.0	370	64	17	MTX, 6MP, BUS	BUS
11	49	M.	14.0	230	22	6	MTX, BUS	BUS, VPA
12	32	M.	7.2	900	310	12	BUS	Cyclic
13	25	F.	7.8	350	670	9	BUS	BUS, TRAMPCOL
14	20	F.	10.0	600	90	30	SXRT	6TG, 6MP
15	41	M.	14.4	1600	54	42	BUS	BUS, 6MP
16	37	F.	12.1	420	73	0	BUS	None
17	34	M.	11.1	220	216	40	BUS	BUS
18	63	F.	11.6	680	45	14	BUS	BUS
19	22	M.	6.3	480	420	2	6TG	6TG, cyclic
20	41	M.	10.2	700	360	8	MTX, BUS	BUS
21	16	M.	6.8	1000	400	0	BUS	Cyclic, TRAMPCO
22	51	F.	8.3	350	180	10	6TG	Cyclic
23	39	M.	11.0	393	147	1	BUS	BUS
24	19	F.	7.8	220	500	40	6TG	6TG
25	32	F.	11.7	230	95	50	6TG	Cyclic
26	57	M.	8.8	560	430	19	6TG	BUS

*N.A.P. = Neutrophil alkaline phosphatase score. Normal range for our laboratory is 37-98 units.

BUS = Busulphan. SXRT = Splenic Irradiation. HU = Hydroxyurea. MTX = Methotrexate. 6MP = Mercaptopurine. 6TG = Thioguanine. Cyclic = Busulphan, mercaptopurine, cyclophosphamide, melphalan, dibromannitol, hydroxyurea, demecolcine, one at a time in 6-week courses. DBM = Dibromannitol. VPA = Vincristine + prednisolone + colapsase (asparaginase), simultaneously. TRAMPCOL = Thioguanine + daunorubicin + cytarabine + methotrexate + prednisolone + cyclophosphamide + vincristine + colapsase, simultaneously. TRAMPCO = Same as TRAMPCOL without colapsase. (VPA, TRAMPCOL, and TRAMPCO were used for treatment of the disease after acute transformation had occurred.)

removal of sutures was delayed. All three patients recovered from their complications. The single instance of venous thrombosis was not associated with thrombocytosis nor with a protracted operation. Nearly all the patients were discharged home 12 to 14 days after splenectomy.

Haematological Changes.—A series of haematological changes was observed with remarkable consistency in almost every patient: the total leucocyte count rose to three to six times its preoperative value, reaching a peak within 24 to 48 hours and returning spontaneously to the original value 48 to 72 hours after splenectomy; the neutrophil alkaline phosphatase score rose to five to 10 times its preoperative value within 72 hours and remained raised for weeks or months; and the platelet count rose slowly, taking seven to 10 days to reach its peak, which was usually four to six times the preoperative value, and requiring weeks or months to return to its former level. These changes will be reported in detail elsewhere. Postoperative platelet counts greater than $1,000 \times 10^9/l$ ($1,000,000/mm^3$) were treated by heparinization, calcium aspirin at low dosage, transfusion to a haemoglobin level greater than 14 g/dl, which was intended to depress the platelet count (Hirsh and Dacie, 1966), early mobilization, and the administration of busulphan. The administration of a single large dose of busulphan (1-1.5 mg/kg body weight)

seven days before operation prevented excessive thrombocytosis in most patients. Warfarin was administered for a few weeks in the older patients with thrombocytosis because of their possibly greater liability to thromboembolic disease, and the administration of oral contraceptives was interrupted in some of the young women until their thrombocytosis subsided.

Haematological Follow-up.—Clinical and haematological control after splenectomy was satisfactory in all patients so long as their C.G.L. remained in the chronic phase. Since control is generally satisfactory in patients in the chronic phase of C.G.L. who have not undergone splenectomy, we cannot claim any improvement in the splenectomized patients. Treatment with busulphan or other drugs in our patients was no more difficult than in non-splenectomized patients and in particular the doses required did not differ significantly. Follow-up haematological values are summarized in table II. Apart from the occurrence of thrombocytosis exceeding $1,000 \times 10^9/l$ ($1,000,000/mm^3$) in 14 patients the figures are unremarkable. The variations in the highest observed total leucocyte counts are attributable to small differences in treatment policy at the different hospitals and to variations in the regularity of outpatient attendances. It remains uncertain if the accepted indications for resumption of interrupted busulphan therapy in patients who have not undergone splenectomy (Galton, 1969) also apply in patients after splenectomy. There are indications that the control of peripheral blood leucocyte levels may be set at a higher level after operation than before it so that leucocytosis alone may not be a valid indication for further chemotherapy. The relative weights to be given to leucocytosis, anaemia, thrombocytosis, or change in the differential leucocyte count remain to be determined.

Effect on Survival and Onset of Metamorphosis.—The survival times of the 26 patients are summarized in table III. The first splenectomy was performed almost nine years before the time of writing and the latest 5.5 months before. Nineteen patients underwent splenectomy within 12 months of diagnosis and 14 within seven months. Since 21 patients remained alive at the time of writing the eventual median survival is unknown. Two of the five deaths were due to intercurrent disease unrelated to C.G.L., and three patients died with uncontrolled C.G.L. in metamorphosis. Two further patients, alive at the time of writing, underwent metamorphosis of their C.G.L. Statistical comparison of these results with the experience of those busulphan-treated patients in the Medical Research Council's study (Medical Research Council, 1968) who, like our patients, had a satisfactory response to initial treatment with busulphan suggested that 12 cases of metamorphosis would have been expected in the period of observation. The difference between

TABLE II—Haematological Values in 26 Patients With Chronic Granulocytic Leukaemia after Elective Splenectomy and while Disease Remained in Chronic Phase

Case No.	Platelets ($\times 10^9/l$)		Total Leucocytes ($\times 10^9/l$)	
	Highest	Lowest	Highest	Lowest
1	350	150	30	15
2	540	150	197	6
3	1,300	270	105	4
4	355	150	214	4.2
5	2,900	210	58	1.4
6	660	260	18	5
7	1,600	700	32	4.7
8	680	210	48	11
9	1,400	160	56	2.9
10	1,200	180	115	6
11	340	65	11	7
12	1,500	44	220	2.5
13	1,500	650	14	6.5
14	4,000	140	43	1.2
15	1,400	310	29	5
16	400	130	17	10
17	300	200	25	7.2
18	2,600	560	74	5.6
19	440	14	130	1.5
20	850	240	57	10
21	2,900	140	30	2.8
22	710	420	20	6.2
23	900	669	40	14
24	1,400	470	100	7.4
25	1,600	310	13	4
26	2,450	1,200	22	19

Values in first 14 postoperative days have been excluded.

TABLE III—Results of Elective Splenectomy in Patients with Chronic Granulocytic Leukaemia at 31 January 1974

Case No.	Time from Diagnosis to Splenectomy in Months (A)	Length of Chronic Phase after Splenectomy in Months (B)	Survival after Metamorphosis in Months (C)	Length of Chronic Phase in Months (A + B)	Survival from Splenectomy in Months (B + C)	Survival from Diagnosis in Months (A + B + C)	Date and Cause of Death
1	13	90+		103+	90+	103+	
2	4	98+		102+	98+	102+	
3	56	43+		99+	43+	99+	
4	0.5	65.5+		66+	65.5+	66+	
5	30	25+		55+	25+	55+	
6	25.5	26.5+		52+	26.5+	52+	
7	26.5	17.5+		44+	17.5+	44+	
8	9.5	22	8	31.5	30	39.5	7/12/73, uncontrolled leukaemia
9	4.5	34.5+		39+	34.5+	39+	
10	14.5	16.5	1.5+	31	18+	32.5+	
11	20	9	1.5	29	10.5	30.5	20/10/73, uncontrolled leukaemia
12	2.5	25+		27.5+	25	27.5	18/1/74, duodenal ulcer
13	6.5	5	14.5	11.5	19.5	26	5/6/72, uncontrolled leukaemia
14	10	15.5+		25.5+	15.5+	25.5+	
15	5.5	17.5+		23+	17.5+	23+	
16	10	11+		21+	11+	21+	
17	6	15+		21+	15+	21+	
18	2	17.5+		19.5+	17.5+	19.5+	
19	4	13.5+		17.5+	13.5+	17.5+	
20	10	4.5+		14.5+	4.5	14.5+	5/10/73, malignant melanoma
21	5.5	6.5	1.5+	12	8+	13.5+	
22	9.5	4+		13.5+	4+	13.5+	
23	4	7+		11+	7+	11+	
24	4.5	6+		10.5+	6+	10.5+	
25	2.5	7.5+		10+	7.5+	10+	
26	4.5	1+		5.5+	1+	5.5+	

the observed (five) and the expected incidence of metamorphosis was significant at the 2% level. It could be argued that our patients were selected, not only by the fact that they had not developed overt metamorphosis before splenectomy but also because mild symptoms and haematological deviations sometimes precede clearcut metamorphosis by a few weeks; the occurrence of such changes might exert a selective effect by preventing splenectomy. This effect can be offset by introducing a four-month correction factor—that is, assuming the splenectomized patients were at risk of metamorphosis for four months less than seemed to be the case. Even with this stringent correction 10 instances of metamorphosis would be expected and the difference between the number observed and expected was significant at the 5% level (see Statistical Appendix).

Discussion

Because of the rarity of C.G.L. and the relatively long course of the disease this study, like others in C.G.L. (Medical Research Council, 1968), has taken several years and the median survival of the patients has not yet been reached. Long-term clinical studies in the acute leukaemias may be affected by new developments in supportive therapy—for example, improved antibiotics and granulocyte transfusions—during the course of the study. In the chronic phase of C.G.L., however, supportive therapy is of such minor importance that advances in this field are unlikely to have had any effect. Our study was uncontrolled but the patients treated by busulphan in the Medical Research Council's trial (1968) provided 50 controls which seem reasonably comparable in that the diagnosis of C.G.L. was not in doubt, the initial response to busulphan was satisfactory, and they were not older than 65 years. The different experience of metamorphosis between splenectomized and non-splenectomized patients cannot be attributed only to random differences between the two series ($P < 0.05$), but it could be due to systematic differences in the type of patient admitted to the two series because they were not separated by randomization. We are not aware of any selection of patients in our study other than exclusion of patients because of unsatisfactory response to initial treatment, age, or illness in addition to C.G.L. In C.G.L. there are no features known to be associated with long survival that would have made it possible deliberately to select for splenectomy patients who were likely to fare particularly well. We have recently faced for the first time the question of exclusion from our study of patients with histologically proved myelofibrosis in C.G.L. (Grainick *et al.*, 1971). At present, it seems best to accept myelofibrosis as a relative contraindication to elective splenectomy in C.G.L.

It may be surprising that while in five of our patients the disease underwent metamorphosis no patient developed myelofibrosis. Only further follow-up of these and other cases can tell whether or not early splenectomy may favourably influence C.G.L., not only as regards the occurrence of metamorphosis but as regards the complicating feature of myelofibrosis.

The most probable explanation of our results is that splenectomy postponed the metamorphosis of C.G.L. from a chronic to an acute phase. The results do not prove this hypothesis beyond reasonable doubt but they do show that splenectomy in C.G.L. is reasonably safe and without obvious adverse effects on prognosis, and they support the need for the controlled clinical trial of splenectomy in C.G.L. which the Medical Research Council has inaugurated. We cannot agree with the recommendation (Schwarzenberg *et al.*, 1973) that patients with C.G.L. who undergo splenectomy must be operated upon and nursed in an aseptic environment. The mechanism whereby splenectomy might postpone the metamorphosis of C.G.L. is unknown, but removal of a site particularly suitable for the development of aneuploid cell clones with anaplastic properties is a possible hypothesis. Metamorphosis has been observed from five to 22 months after splenectomy so there is as yet no clear analogy with the complete resection of a primary tumour before meta-

stasis has occurred. None of the eight patients who underwent splenectomy more than two years before the time of writing developed metamorphosis and their follow-up is therefore of special interest. A further possibility is that splenectomy favourably influences the course of C.G.L. merely by the removal of a significant mass of leukaemic tissue. This seems unlikely unless this effect is directly related to the relatively early stage of the disease. In most of our cases the spleen was relatively small, and the experience of others who have removed much larger spleens from patients later in the course of the disease suggests that this explanation is not a reasonable one.

Our results do not yet establish whether prior splenectomy significantly improves the duration of life after metamorphosis has occurred. Two patients (cases 8 and 13), however, survived for eight and 14.5 months respectively and both had an acute type of metamorphosis with numerous circulating primitive cells. There seems no doubt that the quality of life after metamorphosis was improved. Apart from the absence of distressing symptoms of splenic origin, which are very common during this phase, comparison with the serial haematological charts (Spiers and Galton, 1970) of non-splenectomized patients with C.G.L. in metamorphosis shows that the splenectomized patients needed fewer transfusions of blood and platelets. Tolerance to antileukaemic chemotherapy seems to have been improved and the patients spent less time in hospital than is usual after C.G.L. has become acute. Our experience of splenectomy in C.G.L. has shown it to be a reasonable procedure and its apparently beneficial effects justify its further evaluation by a controlled clinical trial.

We thank Professor J. V. Dacie and Professor Sir Richard Doll for helpful discussion and criticism. We acknowledge with thanks the help and co-operation of Professor R. M. Mitchell and Mr. J. J. Shepherd, who performed some of the splenectomies, and of Professor D. G. Penington and Dr. H. G. Wilson, who kindly provided details of the haematological follow-up in some patients.

Statistical Appendix

The test used was based on Mantel's (1966) idea of multiple contingency tables. When in one of our splenectomized patients with C.G.L. in its chronic phase the disease undergoes metamorphosis a 2×2 table is set up, using for comparison the data from the Medical Research Council working party's report (Medical Research Council, 1968) excluding those patients who failed to achieve initial satisfactory response to busulphan. If the patient in

	M.R.C Patients Treated with Busulphan	Present Series	
Disease already in metamorphosis			1
"At risk"			M + S - 1
	M	S	

our series whose C.G.L. underwent metamorphosis was then x months after diagnosis the numbers "at risk" are: M, the number of patients in the M.R.C. study who would have been eligible for splenectomy less than $(x-4)$ months after diagnosis and who were still under observation and not in metamorphosis x months after diagnosis, and S, the number of patients splenectomized less than $(x-4)$ months after diagnosis who were still under observation and whose disease had not undergone metamorphosis x months after diagnosis. The no-interaction hypothesis, which postulates that splenectomy has no effect, may be tested by calculating the observed and expected instances of metamorphosis and the variance of their difference for the top rows of each such table. Summation of all such tables then yields:

	M.R.C. Patients	Present Series
Sum of observed numbers	35	5
Sum of expected numbers	29.84	10.16
Ratio	1.17	0.49
Difference, D		5.16
Variance of difference, s^2		7.40
$(D/\sqrt{s})/s$		1.71
Significance level by 1-tailed normal approximation $P < 0.05$		

In selecting control patients from the M.R.C. series a four-month correction factor was introduced to compensate for possible selection of patients in the splenectomy series, in that the appearance of unexplained symptoms or of anaemia might have prevented splenectomy in a patient under our care. Such symptoms can occur up to three or four months before metamorphosis of C.G.L. is haematologically apparent and could have prevented a patient whose C.G.L. was destined to undergo metamorphosis in the near future from being entered into our series. In fact, no patients were actually excluded on the basis. If the correction factor of four months is omitted the results then develop a higher level of significance ($P < 0.02$), since about 12 cases of metamorphosis of C.G.L. would then have been expected in the splenectomized patients. The time when splenectomy was undertaken depended upon the time taken by each of our patients to achieve clinical remission of his C.G.L., but this is unlikely to have introduced a bias since in the M.R.C. series no correlation existed between the time taken to achieve remission and ultimate prognosis.

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Pituitary Sensitivity to 50 μ g LH/FSH-RH in Subjects with Anorexia Nervosa in Acute and Recovery Stages

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British Medical Journal, 1975, 1, 179-182

Summary

Gonadotrophic output was measured in response to a 50- μ g dose of luteinizing hormone/follicle stimulating hormone-releasing hormone (LH/FSH-RH) in subjects with anorexia nervosa. A diminished response was found in subjects of low body weight, and in some a response occurred with increments of plasma FSH greater than those of LH. With restoration of body weight the response to the releasing factor was similar to that usually observed in healthy men and women.

Introduction

Primary anorexia nervosa occurs most commonly in adolescent

girls and is characterized by loss of weight and secondary amenorrhoea. It is generally considered that the disorder is psychologically precipitated and involves mechanisms concerned with the output of gonadotrophins (Crisp, 1967; Russell, 1970). When much weight is lost gonadotrophin and gonadal steroid levels are low but recover as weight is restored (Marshall and Russell Fraser, 1971; Beaumont et al., 1973; Crisp et al., 1973) though cyclical bleeding in women rarely resumes until normal weight is regained and may even then be delayed (Kay and Leigh, 1954; Crisp and Stonehill, 1971).

The present investigation was undertaken to assess the sensitivity of the anterior pituitary to gonadotrophin-releasing hormone (luteinizing hormone/follicle-stimulating hormone-releasing hormone (LH/FSH-RH)) in patients with anorexia nervosa at different stages of treatment.

Patients and Methods

Twelve women and two men with primary anorexia nervosa of at least six months duration and of the "abstaining" kind (Crisp, 1967) were studied at various stages of their treatment at St. George's Hospital, London. Four of the women and one man were tested on two or more occasions, once at a low weight and again when normal weight had been regained. The treatment regimen for these patients aimed at restoring their weight to the population mean norm (Kemsley, 1952) for their sex, height, and age at onset of the illness ("target weight"). Relevant details of the patients are shown in table I.

LH/FSH-RH Test.—Blood samples (5 ml) were taken before and at various intervals after an intravenous injection of 50 μ g LH/FSH-RH (Akande et al., 1972) (see table II). The blood was collected into heparinized tubes and centrifuged within an

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