women who were taking oral contraceptives did not have a higher neutrophil count than those who were not and both groups had counts which were significantly higher than those of the men. Our observations contrast with those of Pincus (1965), who showed that oral contraceptives raised the neutrophil count. His subjects were taking preparations with 75–150 µg of oestrogen, however, whereas the oral contraceptives taken by our subjects contained 30–50 µg of oestrogen and also usually had a lower progestogen content.

Our results also confirm earlier observations that the neutrophil count rises in the afternoon (Garrey and Bryan, 1935; Kennon *et al.*, 1937). We therefore suggest that it is important to consider both the sex and the time of day when deciding whether a neutrophil count is lower than normal. The lower limit of normal which is widely used is 2.5×10^9 neutrophils/l ($2500/\text{mm}^3$). Our results show that this value is too high for either sex, particularly in the morning, when—for example, 31% of our normal men had counts below this level.

Variation of the neutrophil count may also occur on a racial basis. For example, Shaper and Lewis (1971) have observed a mean neutrophil count of $1.96 \times 10^9/\text{l}$ ($1960/\text{mm}^3$) in 250 male African blood donors. This value is lower than the mean value which we found in this study of Caucasians of European origin.

The values we have observed for the lymphocyte, monocyte, eosinophil, and basophil counts are similar to those in previously published series (table III), and we have also confirmed earlier observations that the basophil count rises in the afternoon (Finch, 1972). The correlation which we have noted between the monocyte and the neutrophil count was previously reported by Twomey *et al.* (1973). This interesting correlation is consistent with the suggestions that neutrophils and monocytes either have a common precursor or have similar regulatory mechanisms.

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Postoperative Management after Thymectomy

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Summary

This paper reports a retrospective study of the preoperative and postoperative management of 28 patients who underwent thymectomy between 1956 and 1973. Patients who received postoperative artificial ventilation were compared with the group who did not with respect to sex, age, severity of disease, preoperative vital capacity, and thymic histology. Evidence is presented that postoperative artificial ventilation is required when the preoperative vital capacity with the patient on optimum anticholinesterase treatment is less than 2 litres. Additional features associated with a probable need for

artificial ventilation were the presence of a thymoma, bulbar symptoms, especially dysphagia, and age over 50 years. These should be taken into account in any patient whose vital capacity is close to the critical level of 2 litres. When postoperative ventilation was required it was usually necessary for 12 days or more, and tracheostomy should therefore be done at or before thymectomy. Most patients in this series received the same dose of anticholinesterases after operation as before it and no evidence was found of a sudden decrease in requirements for anticholinesterase therapy. Two patients did not, and in them a myasthenic crisis was precipitated. We propose that the preoperative drug regimen can be continued in the immediate post-thymectomy period, allowing selection of patients for tracheostomy and artificial ventilation primarily on the basis of the preoperative vital capacity.

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Introduction

Though there is general agreement on the value of thymectomy in myasthenia gravis there is controversy about the immediate postoperative management. A postoperative mortality of 10% in the earlier years led to the adoption of regimens such as that of Osserman and Jenkins (1971), who advocated routine

tracheostomy and ventilation plus the withdrawal of anticholinesterase therapy, which reduced the postoperative mortality to 2%. Other workers, including Schwab *et al.* (1964), Mulder *et al.* (1972), and Crawford (1971), have used different and less extreme regimens but have not detailed the criteria they use to determine the need for artificial ventilation. Havard (1973) thought routine tracheostomy and ventilation unnecessary but advised tracheostomy at the time of thymectomy if the preoperative vital capacity was "seriously reduced." He, however, recommended the withdrawal of anticholinesterases until clinical evidence of their need became apparent.

A retrospective study of patients with myasthenia gravis who have undergone thymectomy in this centre has therefore been undertaken in an attempt to formulate a policy for the preoperative and postoperative management of such patients, particularly with respect to the need for tracheostomy and artificial ventilation and the use of anticholinesterases.

Patients and Methods

The records of all cases diagnosed as myasthenia gravis since 1956 were reviewed and 54 were found in which the diagnosis was certain. Thirty patients had undergone thymectomy and adequate information was available on 28 of them.

The indications for thymectomy during the survey period were either increasing incapacity despite medical treatment, irrespective of age or sex, or the presence of a thymoma. All but one of the patients had undergone thymectomy within five years of onset of the disease. Ventilatory incapacity was not regarded as a contraindication to the operation and three patients in the series had already required artificial ventilation before thymectomy. One patient was pregnant at the time of thymectomy.

Most of the thymectomies were performed via a sternum-splitting incision and a few patients had a thoracotomy (usually when a thymoma was suspected); later an approach through the bed of the second rib anteriorly was adopted. Postoperatively the patients were managed in the respiration unit jointly by neurologists and anaesthetists. There were no postoperative deaths—that is, within three weeks of the operation.

Fourteen of the 28 patients did not require artificial ventilation though one of these had a tracheostomy at the time of thymectomy. Of the remaining patients 13 had artificial ventilation via a tracheostomy and in one an endotracheal tube was used.

The 14 non-ventilated and 14 ventilated patients were compared with respect to sex, age, distribution of disease, preoperative vital capacity, and thymic histology. Drug management in both groups in the immediate preoperative and postoperative periods was also reviewed.

Results

SEX AND AGE

Of the 28 patients 19 were female, 8 (57%) of the nonventilated group and 11 (79%) of the ventilated group. The average age of the patients in the ventilated group was 45.4 years (range 21–68 years) and in the nonventilated group 32.5 years (range 17–65 years). Only one of the patients in the non-ventilated group was over 50 years of age, whereas in the ventilated group eight were 50 years of age or over.

DISTRIBUTION OF MYASTHENIA

The distribution of the myasthenia was used as an index of its severity using the classification of Osserman (1958) as follows: grade I, ocular involvement alone; grade IIA, mild generalized myasthenia including ocular involvement; grade IIB, moderately severe generalized myasthenia, usually with some bulbar

involvement; grade III, acute severe myasthenia developing over a period of weeks or months with severe bulbar involvement; grade IV, late severe myasthenia, with marked bulbar involvement. No patient with bulbar involvement was included in grade IIA. The numbers of patients in each grade in the non-ventilated and ventilated groups are shown in table I.

TABLE I—Severity of Myasthenia Gravis in Ventilated and Non-ventilated Patients according to Osserman's (1958) Classification (See Text).

	Grade					Total*
	I	IIA	IIB	III	IV	
No. of ventilated patients ..	1		6	6		13
No. of non-ventilated patients ..		8	5			13

*Excludes one patient in each group asymptomatic at time of thymectomy. (See text.)

Two patients were asymptomatic preoperatively and were found to have a thymoma at exploration for a mediastinal mass detected on routine chest x-ray examination. Both subsequently developed myasthenia gravis. One of these patients was given tubocurarine during anaesthesia and required artificial ventilation after failing to breathe spontaneously on completion of the operation. The patient in grade I underwent thymectomy because preoperative investigations suggested the presence of a thymoma. This patient was one of the earliest to have thymectomy and the sternum was split through an extensive submammary incision. Postoperatively a pneumothorax developed, and though artificial ventilation was given the problem was primarily pulmonary and not related to the myasthenia per se. None of the patients in grade IIA required artificial ventilation but all the patients in grade III and just over half of those in grade IIB were given artificial ventilation. Therefore, 71% (12 out of 17) of the patients with bulbar involvement in this series required artificial ventilation.

PREOPERATIVE VITAL CAPACITY

In cases in which the vital capacity had been recorded the reading as near as possible to the date of the operation was selected. The patients had been admitted to hospital several days before thymectomy and were having anticholinesterases at the time of measurement. The vital capacity was recorded at least once daily, and the usual practice is to select the best of three consistent readings. The vital capacity of the patients in the non-ventilated and ventilated groups arranged in chronological order of operation is shown in the fig.

With one exception all the patients requiring postoperative ventilation had a preoperative vital capacity of 2 litres or less.

None of the patients whose vital capacity was greater than 2 litres required ventilation. The one exception occurred in 1957 in a man who had been started on an inadequate dose of pyridostigmine only four days before the thymectomy and who had received no anticholinesterase therapy for 24 hours post-operatively. A myasthenic crisis developed and he required artificial ventilation.

THYMIC HISTOLOGY

Three of the 14 patients (21.4%) in the non-ventilated group had a thymoma and all were suspected preoperatively (see table II). In the ventilated group nine of the 14 patients (64.4%) had a thymoma and six were suspected preoperatively. Seven of the nine patients with a thymoma in the ventilated group were female. The frequency of thymoma (42.9%) in the operated group as a whole was much higher than is usually reported.

TABLE II—Thymic Histology in Ventilated and Non-ventilated Patients

	No. of Ventilated Patients	No. of Non-ventilated Patients
Normal		4
Hyperplasia	5	6
Thymoma*	9	3
Not identified		1
Total	14	14

*One malignant thymoma in each group.

DRUG MANAGEMENT

No rigid drug regimen had been used in either group. Generally anticholinesterases were discontinued the night before the operation or the morning of the operation. In many patients anticholinesterases were reinstituted within a few hours of operation by the oral or intramuscular route. At least two patients required artificial ventilation within 48 hours of the operation because of a myasthenic crisis. One had no anticholinesterases for 24 hours postoperatively and the other had approximately half of the preoperative dose on the basis that there would be increased drug sensitivity in the immediate postoperative period. Drug treatment was continued even in those patients receiving artificial ventilation, partly to aid weaning and partly to increase the patients' comfort by enabling movement in bed.

Discussion

Except for the recommendation that the operation should be carried out in a centre where physicians, surgeons, anaesthetists, and nursing staff are familiar with the problems of pre-operative and postoperative care there is no general agreement about the management of the patient with myasthenia gravis subjected to thymectomy. Divergence of opinion is centred mainly on the need for tracheostomy and artificial ventilation and the immediate postoperative drug regimen. Osserman and Genkins (1971) consider tracheostomy, mechanically controlled or assisted ventilation, and the withdrawal of anticholinesterase medication in the immediate postoperative period essential features in the management. In contrast, Crawford (1971) did not use artificial ventilation routinely and found that it was required for only two patients out of 41. Only one of these patients required tracheostomy. Between these extremes Schwab *et al.* (1964) ventilated patients only when necessary but gave no criteria for selecting such patients. In their series tracheostomy was a routine procedure unless the disease was "extremely mild." Kirschner *et al.* (1969), reporting 21 cases

of transcervical thymectomy, recommended routine tracheostomy for thymectomy and all "major surgery" but reserved artificial ventilation for patients breathing inadequately after operation. They did not, however, define inadequate breathing. Mulder *et al.* (1972) considered routine tracheostomy unnecessary and advised artificial ventilation postoperatively when the vital capacity was less than 1 litre. Using this criterion they found that ventilation was necessary in 50% of their cases.

Review of the present series of 28 cases including severely and moderately severely affected patients suggests that routine tracheostomy and artificial ventilation are not essential for every myasthenic patient subjected to thymectomy. In this series these procedures were adopted in only 50% of the cases. In retrospect artificial ventilation might have been avoided in a further three cases. One patient developed a pneumothorax which was not immediately recognized, another was an asymptomatic patient who was given a standard dose of tubocurarine, and a third was inadequately stabilized on anticholinesterases before operation. With present practice, therefore, more than 50% of the patients might be spared tracheostomy with or without artificial ventilation. The likelihood of this being so is increased with the use of the newer surgical approaches to thymectomy. Thoracotomy and sternal splitting seriously interfere with the thoracic cage and postoperative pain is considerable. Both these factors lower the vital capacity and reduce the efficiency of respiration. The newer incisions—namely, transcervical thymectomy and the approach via the second rib—are less traumatic, give little postoperative pain, and reduce the length of the operation. Nevertheless, these incisions are usually contraindicated when a thymoma is suspected preoperatively, particularly when the mediastinal mass is large or low-lying anteriorly or both.

The anticholinesterase drug regimen in the immediate post-operative period is complementary to the use of artificial ventilation and neither can be considered in isolation. If it is intended to withdraw drugs postoperatively tracheostomy at thymectomy should be a routine procedure, and Havard's (1973) recommendation to use preoperative vital capacity with the patient stabilized on anticholinesterases as a criterion for tracheostomy when these drugs are then withheld postoperatively does not seem safe. Reasons given for withdrawing or reducing the dose of anticholinesterases include increased bronchial secretions, increased sensitivity to anticholinesterases, and temporary remission of the disease in the immediate post-operative period. In this series we found no evidence to support these contentions. Withdrawal or reduction of drugs led to myasthenic crises in two of our patients and the majority continued on the same dose of anticholinesterases in the immediate postoperative period. The need for and the duration of artificial ventilation are increased by the withdrawal of drugs, and in addition patients may be left quite weak. Routine tracheostomy and artificial ventilation carry risks, admittedly small in experienced hands. Infections, mechanical problems with ventilators, scarring after tracheostomy, particularly in young women, and discomfort are hazards and disadvantages not to be lightly discounted. Therefore, a safe policy for selecting patients for tracheostomy and artificial ventilation has obvious merit.

If it is accepted that there is no need to withdraw drugs in the immediate postoperative period we believe it is possible to select those patients who will and those who will not require tracheostomy and artificial ventilation. The most important factor in such selection is the preoperative vital capacity with the patient stabilized on anticholinesterases. Patients whose preoperative vital capacity is greater than 2 litres are unlikely to have postoperative respiratory problems, but if the pre-operative vital capacity is consistently below 2 litres then we believe that tracheostomy at the time of thymectomy and artificial ventilation are indicated. With the exception of one early case, the management of which would not now be regarded as adequate, this guide would have predicted the requirement for artificial ventilation correctly in all the patients in this series.

In marginal cases the presence of a thymoma, age over 50 years, bulbar involvement, and a thoracotomy or sternum-splitting incision are other factors favouring the need for tracheostomy and artificial ventilation. In this series patients who had artificial ventilation required it for more than 12 days (with the exception of one patient given tubocurarine), and we believe that if artificial ventilation is predicted as being necessary then tracheostomy, if not already done, should be performed at the time of thymectomy to spare the patient days of discomfort with an endotracheal tube.

We suggest that there are two safe policies for the management of the patient with myasthenia gravis subjected to thymectomy. The first is routine tracheostomy and artificial ventilation, which allows withdrawal of anticholinesterases in safety and avoids the problem of manipulation of drugs in the immediate postoperative period. In our opinion, however, this policy entails needless tracheostomy and ventilation in many patients. The second safe policy described here is to continue the preoperative drug regimen in the postoperative period and select patients preoperatively for tracheostomy and artificial ventilation principally on the preoperative vital capacity. Compromise

within these two policies is likely to lead to emergency intubation and tracheostomy in unfavourable circumstances.

We wish to acknowledge the skill and attention of our surgical colleagues the late Mr. L. Pile, Mr. A. J. Gunning, and especially Mr. C. Grimshaw, who performed most of the thymectomies and introduced the new surgical approach mentioned in the text. We also thank the staff of the respiration unit at Churchill Hospital who helped with the care of these patients.

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Acute Lymphoblastic Leukaemia: A Heterogenous Disease

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Summary

By using several techniques to detect surface markers on T and B lymphocytes, 11 cases of acute lymphoblastic leukaemia (A.L.L.) were studied. In four cases an insignificant number of markers were detected on the lymphoblast populations. In one case a significant number of blasts formed both sheep red blood cell rosettes and Fc rosettes, suggesting a T-cell origin for the neoplastic cells, and in another case the presence of Fc and C3 receptors on the lymphoblast population indicated a B-cell origin. In a further five cases 14-43% of the blasts had detectable surface immunoglobulin. It is concluded that A.L.L. is a heterogeneous disorder, some cases failing to express surface markers and others having either a T- or a B-lymphocyte origin or both.

Introduction

Lymphocytes derived from human bone marrow (B lymphocytes) express on their surface immunoglobulin (Ig) determinants (Pernis *et al.*, 1971), receptors for fixed IgG (Hallberg *et al.*, 1973), and receptors for activated C3 (Bianco *et al.*, 1973). Thymus-derived lymphocytes (T lymphocytes), on the other hand, have an affinity for non-sensitized sheep red blood cells (R.B.C.) (Lay *et al.*, 1971), with some T cells also expressing Fc

and C3 receptors (Dickler *et al.*, 1974). These B- and T-lymphocyte markers have been used by many workers to investigate such neoplasms as chronic lymphatic leukaemia (C.L.L.) (Preud'homme and Seligmann, 1972; Dickler *et al.*, 1973; Ross *et al.*, 1973), acute lymphoblastic leukaemia (Seligmann *et al.*, 1972; Berella and Sen, 1973; Kersey *et al.*, 1973), prolymphocytic leukaemia (Catovsky *et al.*, 1973), and leukaemic reticuloendotheliosis (Catovsky *et al.*, 1974 a; Haak *et al.*, 1974).

Previously we were unable to show T- and B-lymphocyte markers on A.L.L. lymphoblasts (Collins *et al.*, 1974) though several recent reports suggest that some cases of A.L.L. are T-cell neoplasms (Borella and Sen, 1973; Seligmann *et al.*, 1973; Belpomme *et al.*, 1974; Catovsky *et al.*, 1974 b). We described a single case of A.L.L. with two distinct neoplastic populations, one of T-cell and one of B-cell origin (Haegert *et al.*, 1974 a), and report here our recent findings in 11 cases of A.L.L. using four rosetting reactions (Haegert *et al.*, 1974 a), presenting evidence that in six cases the neoplastic cells expressed B-lymphocyte surface markers.

Methods

Peripheral Blood Lymphocyte Preparations.—Peripheral blood from 11 patients, aged 5-62 years, with A.L.L. (see table) was collected into heparinized bottles and the erythrocytes were sedimented with 0.6% dextran. The leucocyte-rich supernatants were centrifuged on a mixture of Ficoll and sodium metrizoate¹⁸ (Thorsby and Bratlie, 1970), and the lymphocytes were collected as a band at the interface. The lymphocyte suspensions were washed three times with Hepes-Hanks's balanced salt solution supplemented with 0.2% bovine serum albumin then made up to a final suspension of 2.0×10^8 cells in Hepes-MEM (Eagle's medium) with 0.2% bovine serum albumine. The final suspensions contained less than 5% nonlymphoid cells.

Rosette Tests.—To detect lymphocytes with affinity for non-sensitized sheep R.B.C. a sheep R.B.C. rosetting technique was used. Fc receptors, C3 receptors, and Ig determinants were detected by rosetting reactions (Haegert *et al.*, 1974 a). For scanning purposes

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