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MACOP-B Treatment for Advanced Stage Diffuse Large Cell Lymphoma: A Multicenter Italian Study

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Abstract—*Seventy-one patients with advanced stage diffuse large cell lymphoma were treated with MACOP-B. Sixty-nine per cent of patients achieved a complete response (CR), 10% a partial remission, while 11% had no response and 10% died because of toxicity. The CR rate was adversely affected by immunoblastic type, poor performance status and bone marrow involvement.*

Two-year survival for all 71 patients was 55% and 2-year disease-free survival (DFS) for the 49 CRs was 73%. Relapses were lower ($P < 0.05$) in patients achieving CR in 8 weeks or less (DFS 83% vs. 59%) and in patients without tumor bulk (DFS 87% vs. 54%).

Overall toxicity was acceptable with mucositis proving to be the most frequent severe side-effect. However, treatment-related deaths were unacceptably high in patients over 59 years of age (30% vs. 7%). Thus for the elderly MACOP-B is potentially lethal and must be used cautiously.

These preliminary results confirm the effectiveness of MACOP-B. The delay of response and/or the presence of tumor bulk may be important prognostic factors in identifying a subset of poor risk patients with a high incidence of relapse.

INTRODUCTION

ADVANCED stage diffuse large-cell lymphoma (DLCL) is a rapidly growing malignancy that was usually fatal 15 years ago [1]. The introduction of the CHOP regimen [2] in the early 1970s and its variants (CHOP-Bleo, BACOP) [3, 4] later on yielded complete remission (CR) rates above 50%; however, only 25–35% of patients treated with such programs were long-term disease-free survivors at 10 years [5].

During the past few years continuous improvement in the treatment of DLCL has been achieved with the introduction of more and more effective combination chemotherapy regimens such as Pro-MACE-MOPP [6], ProMACE-CytaBOM [7], COP-BLAM I [8] and III [9], F-MACHOP [10] and MACOP-B [11].

Among these new regimens, MACOP-B chemotherapy, originally proposed by Klimo and Connors in 1984, possibly gives the most promising results with a reported CR rate of 86% and disease-free survival (DFS) rate of 67% at 5 years in the latest report [12].

MACOP-B is a brief intensive chemotherapy completed in only 12 weeks. Drugs are given on a weekly schedule alternating myelosuppressive and non-myelosuppressive agents, thus allowing frequency and continuity of therapy. As MACOP-B fits well with the Goldie and Coldman somatic mutation hypothesis [13] it should maximize response.

Since June 1986 we have started a cooperative study among various Italian hematology–oncology institutions to evaluate the effectiveness of MACOP-B in the treatment of advanced stage DLCL. MACOP-B has been chosen for several reasons: good results originally reported, a brief chemotherapy regimen and feasibility in an outpatient setting. The aims of our study are:

— to improve the results previously obtained with CHOP-like regimens in patients with advanced stage DLCL

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— to compare the results of MACOP-B obtained in a single institution with those achievable in an Italian multicenter study.

The study is still in progress; the preliminary results for the first 71 patients who completed therapy by December 31, 1987 are the topic of this report.

PATIENTS AND METHODS

Between 1 June 1986 and 31 December 1987 71 patients with DLCL entered the cooperative study. They were followed up through 31 August 1988 or to the time of death.

The criteria for inclusion were: unequivocal histologic diagnosis of diffuse non-Hodgkin's lymphoma of centroblastic, immunoblastic or T-zone cell types according to the Kiel classification [14] or large cleaved, large non-cleaved or immunoblastic types according to the Working Formulation [15]; no prior antilymphoma therapy; age between 13 and 65; performance status <3; no past or present medical history of severe cardiac, renal or hepatic disease; and advanced stage disease. This included stage III and IV, as defined by Ann Arbor Conference Criteria [16] and stage II only if the patients had bulky disease (mass greater than 10 cm in one diameter or more than 0.33 of the chest diameter in the mediastinum) or extensive E lesion. Patients with primary gastrointestinal lymphoma and non-contiguous abdominal lymph nodes involved by the tumor were classified as having stage II E disease and included in the study. Patients were classified as having stage IV disease only if they had either biopsy proved or unequivocal radiologic findings of non-contiguous extranodal disease.

Staging included routine blood chemistry, blood cell counts and differential, EKG, chest X-ray, computerized tomography (CT) of chest, abdomen and pelvis and bilateral bone marrow biopsy in all patients. Percutaneous liver biopsy, gastrointestinal series with endoscopy, lumbar puncture with CSF examination and brain CT scan were performed only when there was clinical concern that liver, GI or CNS involvement was present. Patients with AIDS were not included in the study.

The MACOP-B regimen was given according to the original scheme proposed by Klimo and Connors [11]. The same original dose reduction guidelines based only on granulocyte count were used. Thrombocytopenic patients received all drugs in full doses, but platelet transfusions were used when platelet counts fell to less than 20,000/mm^3. Folinic acid rescue after methotrexate was increased in dose and extended in time in respect of the original study of MACOP-B [11]. Briefly, folinic acid 30 mg was given orally every 6 h for 12 doses beginning 24 h after the methotrexate bolus. From 48 h prior to the methotrexate infusion until the completion of the folinic acid rescue all patients received oral or i.v. hydration of 2000 ml/m^2. Sodium bicarbonate was added (3 g every 6 h p.os) to maintain urinary pH > 7.0. Patients with bone marrow or sinus involvement were given CNS prophylaxis consisting of six doses of intrathecal cytarabine 30 mg/m^2 plus prednisone 25 mg/m^2 given twice weekly during the treatment program, starting after the bone marrow or sinuses were clear of disease. All patients received prophylactic cotrimoxazole and nystatin daily throughout the program; ketoconazole was used only when oral *Candida* mucositis developed.

One month after completion of the MACOP-B patients were revaluated for evidence of residual tumor by repetition of any previously abnormal staging studies including appropriate biopsies. Patients with no evidence of residual disease were judged to have a complete response (CR). Eleven patients with small radiologic residual abnormalities had surgical open biopsy of such lesions to clarify the response to therapy: three patients had abdominal exploration with splenectomy and eight patients mediastinal biopsy. Partial response (PR) and failure were defined using standard criteria. In order to evaluate the prognostic significance of a rapid response to chemotherapy, remission status was also assessed with clinical and radiologic studies between the 8th and 9th week of therapy.

Patients with a complete response at the end of the treatment program received no further therapy. Patients with a partial response received various combinations of radiation and salvage chemotherapy.

Statistical methods

All patients started on treatment were considered evaluable. All patients who died during treatment were considered as being treatment failures even though an autopsy might have shown absence of residual disease. A multivariate stepwise logistic regression [17] was used to assess factors affecting CR. Survival and DFS curves were plotted according to the method of Kaplan and Meier [18]. Statistical significance among curves was determined by the Breslow generalized Wilcoxon test.

Multivariate regression analysis according to Cox's proportional regression model [19] was used to assess independent factors influencing DFS. Long-term complete remission rate was defined as the product of the CR rate multiplied by the DFS rate for patients with CR [11]. This tends to correct for errors in post-treatment assessment of response and deaths due to unrelated causes. All calculations were done by applying the BMDP program (1985), developed at the Health Science Computing Facility, UCLA (NIH) Special Research Resources.

RESULTS

The clinical characteristics of the 71 patients are shown in Table 1. The median follow-up for censored patients was 16 months (range 8–26).

Response to treatment

At the end of MACOP-B regimen 49 patients (69%) achieved a CR, seven (10%) had only a PR and 15 (21%) were treatment failures. In the last group eight (11%) showed a true no-response to MACOP-B and seven (10%) died during treatment because of toxicity. Of the 15 patients with partial or no response at the end of MACOP-B only two achieved a CR with salvage radiotherapy but both of them had only small residual nodal disease. The remaining 12 patients progressed despite a variety of salvage chemotherapies.

Of the 49 patients who achieved CR, 32 (65%) did so in the first 8 weeks of therapy. Twenty-three patients were in PR at the 8th week and 13 were converted to CR in the further 4 weeks of therapy. None of the two patients with no response to MACOP-B at the 8th week showed a CR or at least a PR on the completion of the therapy. Four CRs at the end of MACOP-B were not evaluated at the 8th week of therapy.

Table 2 shows the response rate among various subsets of patients.

There were no differences in response rates according to pretreatment clinical features traditionally bearing adverse prognostic significance such as B symptoms, bulky disease, E lesion, increased LDH level, older age. However the complete remission rate was adversely affected by histology, performance status and stage of disease.

There was a trend for stage IV patients without bone marrow (BM) involvement to have a lower CR rate than stage II and III patients, however the differences were not significant ($P = 0.07$). Whereas those with BM involvement did significantly worse: only one of eight patients achieved a CR. Apart from BM no other site of extranodal involvement seems to have a poor prognostic significance, however the numbers are not large enough for a definite conclusion. A multivariate regression analysis confirmed the independent prognostic value for achieving a CR of BM involvement, histology and performance status.

Survival and disease-free survival (DFS)

With a median follow up of 16 months from initiation of treatment the actuarial overall survival for all 71 patients was 55% (Fig. 1).

The DFS for the 49 CRs was 73% with a median off-therapy follow-up of 12 months (Fig. 1).

Twelve patients experienced relapses. All relapses occurred in the first 9 months of follow-up with a median time to relapse of 4 months.

No statistically significant differences in relapse rates were seen when outcomes were analyzed according to stage, histology, symptoms, E lesion, age, LDH level or performance status. Relapses were seen less often in patients who achieved CR in 8 weeks (DFS 83%) than in patients requiring a longer therapy to achieve CR (DFS 59%) ($P = 0.05$) (Fig. 2). Moreover, patients without bulky disease had significantly better DFS (87%) than those with a large tumor mass (DFS 54%) (Fig. 3) ($P < 0.01$). A multivariate regression analysis showed that both the presence of bulky disease and the rapidity of response are independent prognostic factors for DFS.

The outcome of the 12 relapsing patients was generally poor. Six patients died of lymphoma; four continue to receive treatment and only two are in second CR induced by radiotherapy in the first case

Table 1. Clinical characteristics of 71 patients treated with MACOP-B

		No.	%
Male		41	58
Female		30	42
Age (years)	median	45	
	range	15–65	
Histologic subtype			
cleaved or noncleaved		42	59
immunoblastic		29	41
Constitutional symptoms*	none	36	51
	B	35	49
Stage	II†	31	44
	III	19	27
	IV	21	29
Bulky disease	no	36	51
	yes	35	49
Bone marrow	neg	63	89
	pos	8	11
E lesion	no	49	69
	yes	22	31
Immunology	B	57	80
	T	6	9
	ND‡	8	11
Performance status§	0	23	32
	1	31	44
	2	17	24
LDH(u/l)	mean	582	
	range	91–1800	

*Ann Arbor Conference criteria.
†Bulky or extensive extranodal only.
‡Immunology not determined.
§WHO criteria.

Table 2. Response rates of 71 patients to MACOP-B

		Total No.	CR No.	(%)	PR + NR No.	(%)	P
All		71	49	(69)	22	(31)	
Age (years)	mean		44		45		n.s.
Histologic subtype							
cleaved or noncleaved		42	34	(81)	8	(19)	
immunoblastic		29	15	(52)	14	(48)	<0.01
Constitutional symptoms	none	36	25	(69)	11	(31)	
	B	35	24	(69)	11	(31)	n.s.
Stage	II	31	24	(77)	7	(23)	
	III	19	17	(89)	2	(11)	<0.01
	IV BM*	8	1	(12)	7	(88)	
	IV other†	13	7	(53)	6	(47)	
Bulky disease	no	36	26	(72)	10	(28)	
	yes	35	23	(66)	12	(34)	n.s.
E lesion	no	49	32	(65)	17	(35)	
	yes	22	17	(77)	5	(23)	n.s.
Immunology‡	B	57	43	(75)	14	(25)	
	T	6	3	(50)	3	(50)	n.s.
Performance status§	0	23	19	(83)	4	(17)	
	1	31	22	(71)	9	(29)	<0.01
	2	17	8	(47)	9	(53)	
LDH(u/l)	mean		554		675		n.s.

*BM = bone marrow.
†Other stage IV sites.
‡Immunology not determined in eight patients.
§WHO criteria.

and salvage chemotherapy with mitoxantrone + cisplatin + etoposide in the second.

Of the nine patients with bulky disease who experienced relapses only two presented a localized recurrent tumor in the site of previous bulky disease. One is in second remission induced by radiotherapy (see above) and the second is still receiving a chemotherapy treatment with a partial response. In the remaining seven patients relapses occurred in multiple nodal ± extranodal sites.

Toxicity

Toxicity related to treatment was recorded at each week of therapy according to the WHO grades. The most frequent severe (grade 3 + 4) toxicity proved to be mucositis occurring in 41% of the patients. Mild peripheral neurological (dysesthesia, hypoestesias) toxicity was usually seen in most of the patients (55%) but only three developed severe motor weakness.

There was no hepatic, renal, cardiac and pulmonary toxicity. Serious infections requiring hospitalization occurred in five (7%) patients. Despite the high-dose prednisone treatment only one patient required insulin therapy. One patient developed femoral osteonecrosis 14 months after treatment. There have been seven treatment-related toxic deaths. Three patients died from systemic infections (one fungal, one bacterial and one interstitial pneumonitis due to *Pneumocystis carinii*), two patients died of pulmonary thromboembolism and two over 60 died from metabolic and nutritional complications.

Hematological tolerance has been good. Thirty-four per cent of the patients had a neuthrophil nadir of less than 500/mm^3 and only 3% a platelet count of less than 35,000/mm^3. However, anemia was seen more frequently than with other chemotherapy regimens. It was usually present in the last weeks of therapy and 39% of the patients required PRC transfusions.

Age was a determinant in treatment tolerance. Patients over 59 years experienced more severe toxicity. In this group of patients the treatment-related mortality rate was 30% compared with 7% for patients under 60 ($P = 0.02$).

Fifty-nine (83%) patients were given the full planned 12 treatments. Delays during treatment were kept to a minimum: in fact 77% of patients

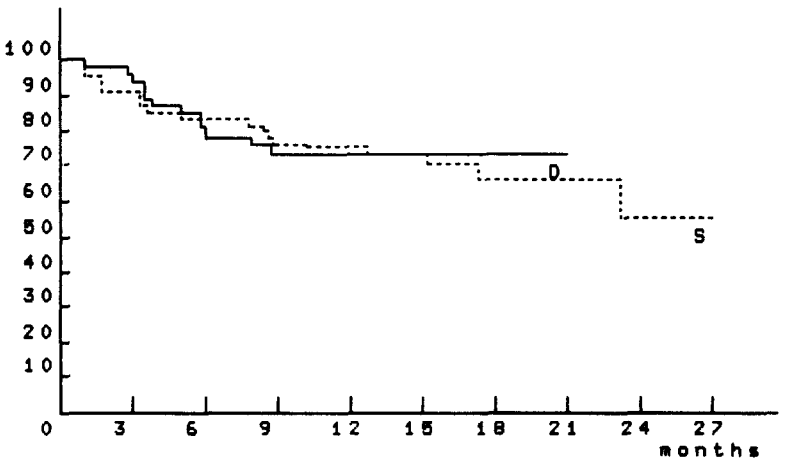

Fig. 1. Survival (S----) in months of the 71 patients treated with MACOP-B and disease-free survival (D——) for the 49 patients achieving CR.

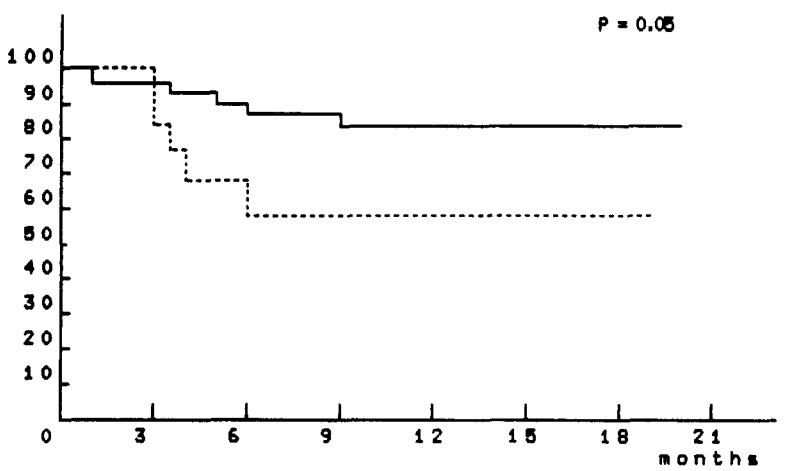

Fig. 2. Disease-free survival in months of the 49 patients achieving CR as determined by the number of weeks of MACOP-B required to achieve CR. CR in 8 weeks or less (——); CR in >8 weeks (----).

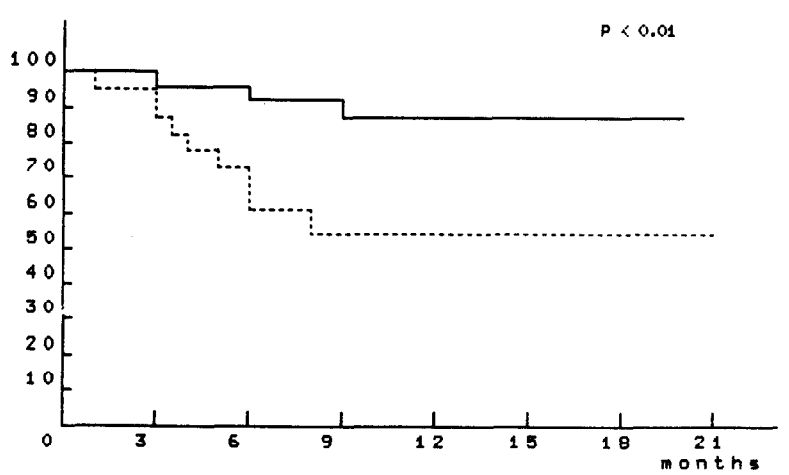

Fig. 3. Disease-free survival in months of the 49 patients who achieved CR as determined by tumor bulk. Patients without tumor bulk (——); patients with tumor bulk (----).

completed treatment within 1 week over the 12 planned.

DISCUSSION

Advanced stage DLCL is now a potentially curable disease with the 'third-generation' programs [20, 21]. However, the results obtained in single institutions with ProMACE-based programs [6, 7], COP-BLAM III [9] and MACOP-B [12] have to be reproduced on a larger scale.

Before June 1986 the patients who were referred to the institutions participating in this cooperative study were treated with CHOP or CHOP-Bleo regimens. In those of the participating institutions whose data (not published) were available, patients with advanced stage DLCL treated with CHOP or CHOP-Bleo had a 65% CR rate and 36% disease-free 5-year survival.

The CR rate of 69% obtained with MACOP-B in this multicenter study does not widely differ from the previous figure with CHOP; however, a 2-year DFS rate of 73% has been achieved. Although the median follow-up time is not long, the DFS curve seems to have reached a plateau. Should these figures be confirmed by a longer follow up, the results obtained with MACOP-B would represent an improvement over those previously achieved with CHOP-like regimens at our institutions, increasing the long-term complete remission rate from 23% to 50%.

In the recently updated Vancouver experience [12] CR rate has been 86% without any significant differences among various subsets of patients.

When compared with this figure our results in terms of CR rate are disappointing. In order to understand this difference various subgroups have been analyzed.

Known prognostic factors such as symptoms, bulky disease, extensive E lesion, increased LDH levels usually predict a poor outcome in patients treated with CHOP or CHOP-Bleo [22, 23]. In our series we have failed to observe any differences in response rates according to these clinical features. Although the sample size of various subgroups might be inadequate to draw definite conclusions it would seem that MACOP-B combination has fared well against these poor prognostic factors.

Although immunoblastic cell type also adversely affected CR rate, bone marrow (BM) involvement clearly emerged as the main indicator of poor prognosis: of eight patients with BM disease only one achieved a CR and subsequently relapsed. Apart from BM positive patients, stage IV patients with other sites of extranodal involvement had a slightly lower CR rate than stage II and III patients but the differences were not statistically significant. In the Vancouver experience the CR rate for BM positive patients was 82%, however a preponderance of relapses in this group (55%) was observed [24].

Thus these data would suggest that patients with BM involvement may be resistant to MACOP-B therapy either because of a low CR rate such as in our experience or because of a high relapse rate such as in the Vancouver experience.

The 73% DFS rate obtained in our series is comparable with 67% for MACOP-B in Vancouver. Although the median follow-up is not long and the above figure could drop, all relapses have occurred in the first 9 months after treatment and 57% of the patients have been off treatment for more than 9 months.

In the current study the only prognostic features affecting DFS were the rapidity of achieving a complete response and the presence of a large tumor mass. The assessment of the response at an intermediate stage of therapy (8th week) gave useful information: 65% of the CRs occurred in the first 8 weeks of therapy and 56% of the PRs at the 8th week were converted to CR within the last 4 weeks of therapy. This might suggest that even the patients who seem to respond slowly could benefit from completing the 12-week program of therapy; instead they fared worse having a less durable response than those who entered CR earlier (DFS 60% vs. 82%) (Fig. 2).

A better prognosis in patients with DLCL who respond more rapidly to chemotherapy has recently been reported with COP-BLAM [25], F-MACHOP [10] and LNH 80 [26] regimens. This has also been observed in other malignancies such as advanced Hodgkin's disease [27] and testicular cancer [28].

In our experience tumor bulk has had no influence on response, but it can predict a worse outcome due to a higher incidence of relapse in patients with a large tumor mass (Fig. 3). Tumor bulk has been found a poor prognostic factor in many series of patients with DLCL treated with regimens such as CHOP [22], CHOP-B [23], BACOP [29], M-BACOD [30] and F-MACHOP [10]. In other trials using newer regimens such as MACOP-B [24] and COP-BLAM III [9], tumor bulk seems to lose its adverse prognostic significance.

We found that by applying a multivariate regression analysis, both the presence of a large tumor mass and the rapidity of response have an independent prognostic value in predicting the chances of relapse. This variability among studies may reflect factors such as patient population, different treatment regimens, sample size and so on; however, this type of analysis should lead to the identification of a poor-risk subset of patients who might benefit from some kind of consolidation therapy in first CR such as radiotherapy on previous site of bulky disease or massive chemioradiotherapy followed by autologous bone marrow transplantation.

The results obtained in the present series, however, represent a drop compared with those reported by Connors and Klimo [12, 24]. An instability of results has been observed in many regimens used in institutions other than the original ones or where longer follow-up data is available [21]. DFS for MACOP-B in Vancouver dropped from the original 88% to 76% and 67% later on when the participation of outside community oncologists increased [12, 24]. Other studies with MACOP-B failed to confirm the Vancouver's results: Memorial Sloan Cattering Cancer Institute and the SWOG reported a lower CR rate of less than 50% [21, 31, 32] whereas other groups achieved better results with a CR rate up to 81% [33] and DFS ranging from 65% [34] to 76% [33]. Patient selection, different numbers of patients with adverse prognostic features, familiarity with the regimen or other factors may play a role in explaining such differences.

In our hands the weekly schedule of MACOP-B proved feasible with 83% of patients given the full planned 12 treatments and delays during treatment were kept to a minimum.

The overall toxicity has been moderate. With regard to cardiac, renal, hepatic toxicities, rate of serious infections and frequency of severe myelosuppression, MACOP-B has proved acceptable in our experience. Although we lengthened the folinic acid rescue, mucositis has proved to be the most troublesome and severe toxicity, as in the Vancouver series. The mortality rate has been 10%. Although in two cases (pulmonary thromboembolism) the contribution of the treatment is questionable, this figure is worrisome. Treatment-related deaths have occurred in almost all therapeutic trials in DLCL ranging from <3% with M-BACOD [35] to as many as 17% of patients in the first report of ProMACE-MOPP [36]. With MACOP-B toxic death rate has stayed at 5% in the subsequent reports of the Vancouver group [12, 24] and at MSKCC [33], but it has been roughly 10% in other experiences with MACOP-B [34, 35].

In our series the risk of morbidity and mortality related to treatment is significantly higher in the elderly. Thus in patients over 59 years of age MACOP-B is potentially lethal and must be used cautiously.

In conclusion this multicenter trial confirms the effectiveness of MACOP-B in the treatment of advanced stage DLCL. A long-term complete remission rate of 50% has been achieved with a brief therapy delivered in most of the patients on an outpatient basis. These results would suggest an advantage of MACOP-B compared CHOP-like regimens, however the discrepancies among studies that have used the third-generation regimens stress the need to apply widely these chemotherapy combinations such as MACOP-B in large scale multicenter trials with a longer follow-up before drawing definite conclusions.

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APPENDIX

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