

Epidemiology, Pathogenesis and Approaches to Management of Follicular Lymphoma

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It has been repeatedly observed that there are marked differences in the proportion of non-Hodgkin's lymphoma (NHL) with follicular histology over different geographic regions, with a high frequency in North America, intermediate frequency through most of Western Europe, and a low frequency among Asian countries. Although now widely accepted, this observation remains unexplained. The aim of the current session is to briefly review the available geographically based incidence data, and examine the known aspects of the epidemiology and molecular pathogenesis of the follicular lymphomas, particularly relating to the involvement of the *bcl-2* oncogene, with a view to illuminating potential explanations for these differences and then exploring how this understanding may influence the therapeutic approach to patients with follicular NHL.

Geographic variation in follicular NHL

For many years it has been recognised that follicular NHL makes up a relatively small proportion of all cases of lymphoma diagnosed within most Asian countries (Table 1). The summary data from many of the larger recent studies reveal that across most nations in this region, only 8–12% of consecutive series of newly diagnosed lymphoma cases

are of follicular histology. Two series^{7,8} with a total of 1756 patients suggests that the proportion may be even lower in Korea; 3.8% and 6.2%, respectively.

These figures contrast dramatically with the relative proportion of 20–33% reported for most industrialised North American and European countries.⁴ In this context, it is interesting to note that data reported from Cape Town, South Africa, conform to the pattern of the European centres with 33% of all lymphomas having follicular histology. Notably, Northern Italy appears to provide an exception to this observation, with only 11% of all lymphomas being of follicular histology.⁴

Although the available data is less complete, the relative frequency of follicular histology among NHL cases in developing nations outside of Asia generally follows that of the Asian countries noted above, with proportions of 16.7% reported in Oman,¹⁶ 8.1% in Pakistan,¹⁷ 13.3% in Nigeria,¹⁸ and 1.5% in Gabon, equatorial Africa.¹⁹ These similar frequencies are despite marked variation in the ethnic background and geographic localisation of these regions, consistent with a dominant effect for environmental rather than genetic influences. This is also consistent with the data derived from Asian emigrants to the United States and their

Table 1: Relative frequency of histologic sub-types of NHL

| A: Asia / India: | | | | | | | | | |
|---|--------------|------|-----------|---------|--------|--------|--------------------|----------|--|
| Reference | Region | Year | No. cases | FSC (%) | FM (%) | FL (%) | All follicular (%) | DLCL (%) | |
| 1 | Japan | 1983 | 604 | ? | ? | ? | 11.6 | ? | |
| 2 | Japan | 1985 | 294 | ? | ? | ? | 10.7 | 46.2 | |
| 3 | Hong Kong | 1984 | 267 | 6.4 | 3.4 | 0.4 | 10.1 | 18.7 | |
| 4 | Hong Kong | 1998 | 197 | ? | ? | ? | 8.0 | 39.0 | |
| 5 | Thailand | 1996 | 1391 | 1.9 | 0.9 | 1.0 | 3.8 | 39.9 | |
| 6 | Thailand | 1998 | 389 | 2.8 | 1.8 | 6.4 | 11.1 | 31.3 | |
| 7 | Korea | 1992 | 290 | 0.3 | 1.4 | 2.1 | 3.8 | 58.3 | |
| 8 | Korea | 1998 | 1466 | ? | ? | ? | 6.2 | 43.7 | |
| 9 | Korea | 1985 | 298 | 0 | 0.7 | 2.7 | 3.4 | 53.7 | |
| 10 | China | 1987 | 192 | 5.2 | 3.6 | 5.2 | 14.0 | 24.5 | |
| 11 | Philippines | 1986 | 262 | 4.2 | 3.8 | 0 | 8.0 | 29.7 | |
| 12 | India | 1985 | 238 | 5.9 | 2.5 | 0.4 | 8.8 | 39.1 | |
| 13 | India | 1985 | 1050 | ? | ? | ? | 10.0 | ? | |
| 14 | Taiwan | 1991 | 636 | 2.9 | 1.8 | 1.8 | 6.3 | 54.9 | |
| B: North America / Europe / South Africa: | | | | | | | | | |
| Reference | Region | Year | No. cases | FSC (%) | FM (%) | FL (%) | All follicular (%) | DLCL (%) | |
| 4 | USA | 1998 | 200 | ? | ? | ? | 32 | 28 | |
| 4 | Canada | 1998 | 200 | ? | ? | ? | 31 | 31 | |
| 4 | South Africa | 1998 | 188 | ? | ? | ? | 33 | 31 | |
| 4 | Britain | 1998 | 119 | ? | ? | ? | 28 | 29 | |
| 4 | Germany | 1998 | 203 | ? | ? | ? | 18 | 30 | |
| 4 | France | 1998 | 192 | ? | ? | ? | 17 | 39 | |
| 4 | Italy | 1998 | 79 | ? | ? | ? | 11 | 45 | |
| 15 | USA - NCI | 1982 | 1153 | 22.5 | 7.7 | 3.8 | 34.0 | 27.6 | |

descendants,²⁰ in which emigrants appeared to maintain the disease risk of their country of birth and early upbringing, whereas the incidence among their children born in the United States approached that of US-born whites.

While these figures allow comparisons of the *relative* proportion of various lymphoma types between countries, they do not provide data on the *absolute* incidence rates. Unfortunately, most of the available population-based incidence figures do not include specific histologic subtyping. Much of the following discussion therefore relies upon application of the above relative proportions observed in the above hospital-based series to population-based overall incidence figures, and thus assumes that the relative distribution of histologic types is representative of that seen in the country as a whole. In the absence of alternative sources of information, and no available data either supporting or refuting such an assumption, the procedure is reasonable for the purposes of the discussion. The other important factor that will have an impact upon these international comparisons is the age-structure of the populations under analysis. As so well exemplified recently by Hakulinen,²¹ the known age-dependent incidence of NHL will result in an apparent higher incidence rate among those groups with older average populations, even in the absence of any intrinsic differences in the risk of each individual within those populations. Thus wherever possible, incidence data should ideally be adjusted to a “world-standard” population. Again, unfortunately this procedure has not routinely been performed on available data, particularly in developing nations, and this influence must also be borne in mind when considering the presented comparisons. However, even allowing for a relatively extreme effect of population demographics, such as that presented by Hakulinen for Quito, Ecuador where the median age of the population is just 20 years, such adjustment to “world standard” population resulted in an increase in less than 50% in the crude incidence rates.²¹ Even the application of such extreme adjustment factors to the presented data for most Asian countries would not significantly alter the conclusions presented.

There is reliable population-based data on specific incidence rates for follicular lymphomas available from the USA. The most recent direct data available for histologic subtypes is from the SEER registry for 1986-1988,²² where the annual rate (per 100,000 population) for follicular small-cleaved cell (FSC) was 1.3, follicular mixed (FM) 0.7, and follicular large-cell (FL) 0.4. Thus the cumulative annual incidence rate for all forms of follicular lymphoma at this time was 2.4 per 100,000 population per year. Within the USA, even allowing for changes in population demographics, disease classification, and changing availability of medical investigations, the overall incidence of NHL has been increasing at about 3.4% per year, with a slightly higher rate of increase observed for the aggressive histologic types, such that the overall rate of increase for the follicular lymphomas is somewhat less at ~2% per year.^{22,23} Thus, the 1990 overall annual incidence rate for the US had risen to 13.9 per 100,000,²⁴ and by implication, the incidence rate for all

follicular NHL may currently be as high as 4.5.

Applying population-based overall incidence figures for NHL to the estimated proportion of cases with follicular histology from the available studies (where more than one study from a given country was available, the mean figure was used) yields estimated annual incidence rates for follicular NHL in Asian countries in the range of 0.15-0.38 (**Table 2**). This is clearly much lower than the incidence rate of 1.3-3.0 seen in the industrialised European and North American countries. Thus it is clear that the relative infrequency of follicular NHL reported from Asian countries is due to a truly low incidence rate; averaging approximately 10% of that seen in North America and most industrialised European nations.

Known epidemiologic factors:

As with the incidence data discussed above, much of the available data dealing with the potentially causative genetic and environmental factors contributing to NHL considers all histologic types as a single entity. Where data specific to risk factors for follicular lymphoma are known they will be emphasised; unfortunately, this is rarely possible.

Immunosuppression: Congenital, acquired, and therapeutic immunosuppression are all clearly associated with greatly elevated risks of NHL.^{25,28,29} These tumours are frequently viral-related and of large-cell, immunoblastic, or Burkitt’s histologic types. In a global sense, immunosuppression due to HIV/AIDS makes a significant contribution to the observed increasing incidence of NHL. Yet, at least in the United States, where accurate figures are available, the incidence of non-AIDS-related NHL is also rising significantly.^{22,25,27,28,30} However, there is no evidence that follicular lymphomas are observed with any increased frequency in this patient group, and there is no data implicating immunosuppression (in any form) with the occurrence of follicular NHL.

Table 2: Incidence rates for overall NHL and follicular histologic types by country.

| Country – Region [reference] | Overall NHL rate | Derived Incidence Follicular NHL |
|---------------------------------|------------------|----------------------------------|
| Japan – Miyagi [22]* | 2.5 | 0.28 |
| Japan – Osaka [22]* | 3.4 | 0.38 |
| India – Bombay [22]* | 2.3 | 0.20 |
| Thailand – Khon Kaen [25]* | 3.1 | 0.23 |
| Thailand [26]* | 2.1 | 0.15 |
| China – Qidong [25]* | 2.4 | 0.34 |
| Philippines [26]* | 3.5 | 0.28 |
| Canada – Quebec [25]* | 11.1 | 3.44 |
| Canada – British Columbia [22]* | 7.8 | 2.42 |
| Germany – Hamburg [27]* | 2.9 | 0.52 |
| UK [24]† | 12.2 | 3.42 |
| France [24] † | 13.2 | 2.24 |
| Italy [26]* | 6.53 | 0.72 |

* - adjusted to “world standard” population. † - adjusted to similar age-standardised population - see reference for details.

Predisposing medical conditions: There are a small number of uncommon medical conditions known to be associated with a moderately increased risk of NHL. These include Sjögren's syndrome and other autoimmune connective tissue disorders, Hashimoto's thyroiditis, coeliac disease, chronic *Helicobacter pylori* gastritis, and rheumatoid arthritis with or without Felty's syndrome.²⁵ Broadly, each of these conditions may be considered to represent a form of chronic antigenic stimulation, and the resulting instances of NHL are often organ-confined, except for those complicating rheumatoid arthritis where therapeutic immunosuppression also contributes.²⁹ More provocatively, a number of recent cohort and case-control studies have examined the possible relationship between adult-onset diabetes and risk of NHL with four of the nine studies suggesting a positive association with the most reliable estimate of likely relative risk (RR) ~2-fold.^{31 and references therein} In the context of this discussion of geographic differences in incidence, this observation may potentially provide some explanation for the variability in overall incidence of NHL between industrialised and developing nations. Again, none of the above disorders have been specifically associated with an increased risk of follicular NHL.

Blood transfusion: While the initial small studies had suggested an association between previous blood transfusion and an increased risk of subsequent NHL,³²⁻³⁵ the more rigidly designed nested case-control study by Adami *et al*³⁶ failed to verify any such association (RR 0.93).

Herbicides & pesticides: There have been numerous studies of this issue with a general consensus emerging that high-level or prolonged exposure to these classes of substances is associated with a moderately increased risk of NHL; most studies reporting RR values in the range of 1.3-2.5. However, the specific agents of agents responsible have not been definitively identified. Scherr and Mueller²⁵ thoroughly reviewed the 31 available studies of pesticide and herbicide exposure amongst farmers and related industries up to 1996, noting that 20 of these reported a statistically significantly increased risk of NHL. In conclusion, they note that individual studies had found significant associations between exposure to the following substances and NHL risk: 2,4-dichlorophenoxyacetic acid, organophosphate insecticides, phenoxy acids, chlorophenols, and 2,3,7,8-tetrachlorodibenzo-p-dioxin.²⁵ Other reviews^{37,38} and more recent case-control studies^{39,40} have similarly supported such a causal association. Unfortunately, the majority of these studies did not distinguish the histologic subtype of incident cases of NHL, but where specifically examined, the risk of diffuse aggressive NHL appeared to be most significantly increased; for example Cantor *et al* reported an overall RR of NHL on 1.2, but a higher value of 2.3 for diffuse histologic subtypes.⁴¹ While the frequency of industrial and domestic exposure to these classes of compounds is significantly more likely in European and other industrialised nations, where overall contribution to the observed rates of NHL are likely to be modest. Further, none of these studies specifically examined any possible association between ex-

posure to these compounds and the risk of follicular NHL.

Diet: This field has received relatively little attention as a possible risk factor for NHL. Given the significant differences between European, North American, and Asian dietary habits, this topic would merit future consideration. Notably, there are at least two studies suggesting that higher levels of milk intake may be associated with increased risk of NHL, with RR values as high as 3.4 for ≥ 2 glasses per day described.^{42,43}

Hair dyes: There have been a number of studies suggesting that prolonged use of hair dyes, particularly permanent and darker coloured dyes, is associated with an increased risk of NHL.⁴⁴⁻⁴⁶ However this association is not uniformly found⁴⁷ and even if present is likely to be responsible for only a small proportion of observed cases. There is no data available of specific risks for histologic subtypes, which may be of interest given the marked variability in exposure to such products across geographic regions and socio-economic strata.

Smoking and alcohol: There are at least four relatively large studies which have consistently reported strong trends for higher rates of NHL amongst smokers; RR values were 1.5,⁴⁸ 1.4,⁴⁹ 2.1,⁵⁰ and 1.9 (but restricted to women).⁵¹ Thus it is highly likely that smoking contributes to NHL risk, but the strength of this association is relatively weak. There is some very provocative preliminary data that suggests that smoking may specifically increase the risk of follicular NHL. This evidence is both direct and indirect. Herrinton and Friedman⁵² specifically examined the relationship between smoking habits and histologic subtypes of NHL in the Kaiser Permanente cohort of 252,836 people in California; while smoking was not associated with an increased risk of NHL generally (RR 1.1; 95% confidence intervals 0.9-1.3), there was a statistically significant increase in the risk of developing follicular lymphoma among both former smokers (RR 1.9) and current smokers (RR 1.4).⁵² Indirect supporting evidence was provided by Nelson *et al*⁵³ who specifically examined risk factors for intermediate-grade NHL, finding no association with smoking habits, consistent with the established influence being restricted to other histologic types. Conversely, Brown *et al* found that the RR was greatest for histologically aggressive subtypes (RR 2.3, versus RR 1.4 overall).⁴⁹ There is no evidence that alcohol consumption increases the risk of NHL.^{48,53-55}

Sunlight: It has been noted that patients with a past history of basal cell or squamous cell carcinoma of the skin are at increased risk of subsequently developing NHL; RR 1.36,⁵⁶ and 1.8,⁵⁷ respectively. Similarly, patients with a history of NHL are at increased risk of subsequently developing primary skin cancers of all histologic types; melanoma (RR 1.7), and squamous cell carcinoma (RR 4.8).⁵⁷ Given the known causal relationship between exposure to sunlight and these primary skin malignancies, the possible role of sunlight exposure has been similarly examined as a possible risk factor for NHL, without identifying any clear association.^{58,59}

While the above studies have identified a small num-

ber of factors clearly implicated in the development of NHL, the relevance of these specifically to follicular NHL is unclear, and the proportion of all observed cases attributable to these established or suspected causative factors is likely to be less than 20%.⁶⁰ Unfortunately, none of these possible risk factors adequately explains even a small portion of the observed differences in the geographic variation in incidence rates for follicular NHL. However, to date each of these potential risk actors has been examined in isolation, without consideration of the possibility that these factors may either act sequentially in a “multi-step” process leading to NHL, or alternatively that there may be synergistic interaction of multiple individually weak lymphomagenic stimuli.

bcl-2 structure and function

Although not the primary topic of discussion, a certain level of understanding of the structure and function of the product of the bcl-2 gene is necessary. There have been many excellent thorough reviews of this area in recent years⁶¹⁻⁶³ which may be useful for further reference. In simplistic terms, bcl-2 is the archetypal member of a growing family of apoptosis-regulating genes. More than 15 members of this family are currently known, and these fall into either apoptotic death-inducing or death-inhibitory classes. The ultimate cellular response to a potentially pro-apoptotic extra-cellular signal is determined by the ratio of anti-apoptotic to pro-apoptotic bcl-2 family proteins. This dynamic balance has been termed the “apoptotic rheostat” and it is mediated by competitive dimerization between selective pairs of antagonists and agonists.⁶² In this context, clearly any genetic changes which alter the level of expression of one or another of this dynamically balanced system will profoundly influence the likelihood of a cell undergoing programmed cell death in response to a given physiologic stimulus. There is a large body of data implicating such alterations in the pathogenesis of follicular NHL.

Involvement in follicular NHL:

The most common non-random chromosomal translocation observed in follicular lymphoma occurring in the United States is the balanced translocation between the immunoglobulin heavy chain (IgH) gene on chromosome 18 and the bcl-2 gene on chromosome 14 resulting in the t(14;18)(q32;q21) and leading to constitutive over-expression of a structurally intact bcl-2 protein.⁶⁴⁻⁶⁶

The vast majority of the observed t(14;18) translocations have breakpoints clustered in one of two sites on chromosome 18. The major breakpoint region (MBR), which is involved in ~70% of observed translocations, is in the untranslated region 30' of the last exon of the bcl-2 gene. The minor cluster region (*mcr*), which accounts for 10-15% of observed translocations, is 30kb downstream of the bcl-2 gene. In the remaining ~15% of patients with follicular NHL, the bcl-2 gene appears to be physically intact using all available methods,⁶⁷ yet there is still over-expression of the protein evident in ~90% of these “germline” cases.⁶⁸ Thus, either through structural chromosomal changes, or as

yet unknown mechanisms, ~98% of all cases of follicular small-cleaved cell lymphoma are associated with bcl-2 protein over-expression.⁶⁹ The frequency of over-expression among FM and FL lymphomas is slightly lower, in the 75–85% range.⁷⁰ These observations provide overwhelming support for the hypothesis that bcl-2 over-expression is involved in the pathogenesis of follicular NHL.

The tight physical clustering of breakpoints within the two defined regions of the bcl-2 gene facilitates effective screening for the presence of the t(14;18) translocation by PCR methodology using paired primers for an IgH J_H consensus sequence together with either MBR or *mcr* sequence.⁷¹ The availability of such sensitive and reproducible PCR methods for detection and localisation of bcl-2 breakpoints has greatly facilitated the further examination of possible geographic differences in follicular NHL.

Geographic variation in bcl-2 rearrangements

As we have established, there is marked geographic variation in the incidence of follicular NHL. However, do cases of follicular NHL from different regions share similar underlying molecular defects? Secondly, how does this influence our considerations of the aetiology of follicular NHL among these geographic regions?

This specific issue was addressed, in part, in the recent study by Segel *et al* from Jerusalem.⁷² They performed PCR for MBR bcl-2 gene rearrangement on follicular NHL specimens from 36 patients, finding 61% positive, a percentage not significantly different from many previous European and North American studies. However, the authors then reviewed all published studies of the frequency of bcl-2 gene rearrangement in follicular NHL up to 1995. To minimise the influence of variability in assay sensitivity between studies, the following discussion is limited to the comparison of PCR results where both MBR and *mcr* loci were examined, and also includes more recent studies, in particular the recent large series from MD Anderson.⁷³

Although there is likely to be some level of variability in the sensitivity of the assays used between laboratories, this will have little impact on the rates of positivity among primary diagnostic tissue samples, as such nodes are invariably heavily infiltrated by the malignant cells. Conversely, whether fresh or archival material is used as the source of DNA will have some influence. As clearly shown by the comparative study of Liu *et al*⁷⁴ the rate of detection of bcl-2 rearrangements will be ~10% lower when applied to archival material due to degradation of the DNA. As PCR products from the *mcr* breakpoints have on average a size ~3 times that of MBR breakpoint products, there will be a proportionately greater loss of sensitivity for rearrangements at the *mcr* locus. Unfortunately the use of frozen versus archival material was variable between studies, and indeed between reports from different geographic regions, with more frequent use of fresh tissues among the North American series (**Table 3**). Allowance for such methodologic variations may increase the true positivity rate for the samples from Asian patients 5–10%, and from European

patients by ~5%. However, notably the series of Loke *et al*⁷⁶ which found a 60% rate of bcl-2 rearrangements among Hong Kong Chinese patients, did use frozen tissue in all cases.

Overall, even allowing for such methodologic differences, these results (Table 3) suggest a gradient in the frequency of bcl-2 gene rearrangements from a relatively low rate of 40–60% among both Asian and European studies, to approximately 80% among the series reported from the USA (60–84%). These differences in the overall frequency of bcl-2 gene rearrangements were evident among both MBR rearrangements (45-50% versus 65%, respectively) and *mcr* rearrangements (3-5% versus 13%, respectively). Ideally, it would be preferable to have available simultaneously processed fresh samples from each geographic region for analysis in a single laboratory, but in the absence of such data, the above comparisons must suffice.

If these apparent geographic variations in the frequency of bcl-2 gene rearrangements in follicular NHL from various regions are confirmed, it would imply that different etiologic factors may be at work in these separate regions, and may suggest the existence of separate pathogenetic processes which each culminate in a morphologically similar, but molecularly distinct, follicular NHL. While this remains speculative, the recent analysis of clinical characteristics and treatment outcome of patients with follicular NHL according to the presence or absence of detectable bcl-2 gene rearrangements by López-Guillermo *et al*³⁰ is also supportive of this concept. They found that patients with germline bcl-2 status were older at diagnosis and had higher serum levels of LDH and β_2 -microglobulin than patients with rearranged bcl-2. More provocatively, while patients with germ-

line bcl-2 had a lower CR rate with therapy, the pattern of the observed relapses was more suggestive of an aggressive NHL with ~40% of patients relapsing within 3 years, but no relapses observed to date beyond 3 years. Although based on a relatively small number of patients, the pattern of relapses appeared distinct from the slow but relentless failure observed for most series of patients with advanced follicular NHL.

Bcl-2 in normal persons:

Based on the above data clearly linking bcl-2 gene rearrangements with follicular NHL, most investigators believed that the detection of such a translocation was diagnostic of NHL, and most frequently was associated with follicular disease. The first study demonstrating conclusively that clonal bcl-2 rearrangements could be detected in the absence of follicular NHL was in 1991 from Limpens *et al* at the University of Leiden.⁸⁷ Using sensitive nested PCR methodology capable of detecting one clonal cell in 200,000, they demonstrated bcl-2 / J_H gene rearrangements in 9 of 16 (56%) lymph nodes with follicular hyperplasia, and in 4 of 8 (50%) of tonsils with follicular hyperplasia.⁸⁷ Since that time at least nine further studies have confirmed this initially unexpected result (Table 4). Excluding the study of Fuscoe *et al*⁹⁵ which used a significantly more sensitive technique (able to detect one clonal cell in 10,000,000), and the study of Ohshima *et al* which used a relatively insensitive single-step method,⁸⁹ overall the positivity rates for the various tissues tested are: bone marrow 14% (11/78),^{87,96} spleen 35% (11/31),⁹⁰ tonsils 40% (12/30),^{87,88} peripheral blood 51% (259/503),^{90-94,96} and lymph nodes with follicular hyper-

Table 3: Frequency of bcl-2 gene rearrangement in follicular NHL from different geographic regions.

| Author [reference] | No. Patients evaluable | MBR+ (%) | <i>mcr</i> + (%) | Total bcl-2 + (%) |
|-------------------------------|------------------------|-------------------|------------------|-------------------|
| Asia: | | | | |
| Mitani [75] | 30* | 12 (40) | 1 (3) | 13 (43) |
| Loke [76]† | 16 | 8 (50) | 1 (6) | 9 (56) |
| Subtotal (Percentage; 95% CI) | 46 | 20 (43; 29 - 59) | 2 (4; 0.5 - 15) | 22 (48; 33 - 63) |
| Europe: | | | | |
| Benítez [77] | 5 | 3 (60) | 0 (0) | 3 (60) |
| Pezzella [78] | 51 | 18 (35) | 3 (6) | 21 (41) |
| Lee [79] | 20 | 7 (35) | 1 (5) | 8 (40) |
| Lambrechts [80] | 21 | 12 (57) | 1 (5) | 13 (62) |
| Poetsch [81] | 28 | 18 (64) | 0 (0) | 18 (64) |
| Séité [82] | 64 | 30 (47) | 8 (13) | 38 (59) |
| Johnson [83] | 50 | 30 (60) | 0 (0) | 30 (60) |
| Subtotal (Percentage; 95% CI) | 239 | 118 (49; 43 - 56) | 13 (5; 3 - 9) | 131 (55; 48 - 61) |
| USA: | | | | |
| Zelenetz [84] | 40 | 22 (55) | 6 (15) | 28 (70) |
| Liu [74] | 48 | 24 (50) | 5 (10) | 29 (60) |
| Gribben [85] | 88 | 56 (64) | 18 (20) | 74 (84) |
| Gulley [86] | 8 | 4 (50) | 1 (12) | 5 (62) |
| Lopez-Guillermo [73] | 139 | 105 (70) | 13 (9) | 118 (79) |
| Subtotal (Percentage; 95% CI) | 323 | 211 (65; 60 - 70) | 43 (13; 10 - 17) | 254 (79; 74 - 83) |

* - restricted to follicular small-cleaved cell and follicular mixed, follicular large-cell not included. † - analysis by Southern blotting only performed.

plasia 58% (11/19)^{87,88} (**Figure 1**). Comparable results have been obtained using FISH methodology in 4 of 32 lymph nodes involved by non-neoplastic lymphoproliferative disorders, with estimates of the frequency of bcl-2 rearranged cells of 2–5%.⁸¹ In comparison, using PCR-based methods, the frequency of these cells containing the bcl-2 translocation appears to be around the level of 1 in 10⁶ to 1 in 10⁴ in most of these studies. However, there have been some suggestions that both the rate of positivity within the whole cohort and the frequency of clonal cells within a single individual may be associated with other known risk factors for follicular NHL, consistent with the premise that cells carrying a bcl-2/IgH rearrangement in normal individuals may be precursor cells which may subsequently give rise to clinical disease.

Relationship between age-related incidence of bcl-2 rearrangement in normal persons and the incidence of follicular NHL:

The relationship between age and the rate of positivity, or frequency of bcl-2 rearranged cells, has been examined in a number of the larger studies. However, it is important to note that all of these have been merely correlative, there are no comprehensive studies with longitudinal assessment of individuals over significant periods of time. Liu *et al*⁹⁰ first observed a higher frequency of bcl-2 positivity in the spleens of people ≥ 30 years of age (11/19; 58%) compared with those less than 30 (0/12; 0%) (*P* = 0.001) and further noted a direct correlation between the frequency of t(14;18) containing cells and increasing age in both peripheral blood lymphocyte samples (*r* = 0.37; *P* = 0.0067) and spleens (*r* = 0.59; *P* = 0.0005). Given that there was no change evident in the number of individual clonal sequences isolated from any given individual with increasing age, this observation was suggestive of the progressive accumulation of cells

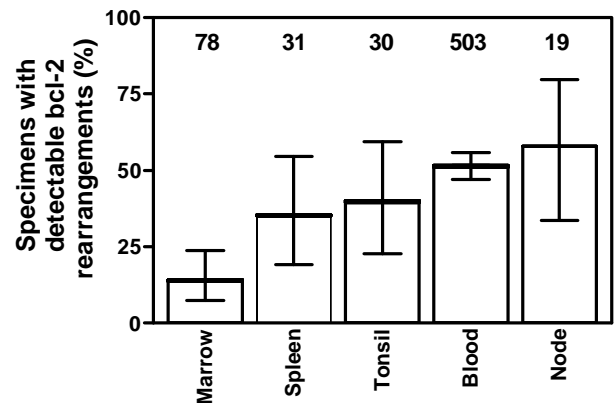


Figure 1: Summary of literature results for percentage of samples from various tissues positive for bcl-2 gene rearrangements from individuals without evidence of lymphoma. Data are presented as percentage and 95% confidence intervals, with total number of samples examined indicated above each tissue. See text for details and references.

from a single clone, rather than acquisition of additional separate clones with increasing age.

A later study by the same group of investigators⁹¹ which examined a larger group of 122 normal volunteers (all aged under 52 years) was unable to show any association between bcl-2 frequency and age, but this may have been due to the lack of truly elderly patients within the cohort, as their earlier study found the most significant increase in rates and frequencies of bcl-2 rearrangements among those over the age of 60 years. Four of the later studies have also explored this issue,⁹³⁻⁹⁶ with only the large study of Li *et al*⁹³

Table 4: Overview of studies of bcl-2 rearrangement in persons without lymphoma:

| Author / region [reference] | PCR method (No. cycles) | Amount DNA used | Tissue | Median age samples (range) | Percent positive | Frequency (per 10 ⁶ cells) | Comments |
|-----------------------------|-------------------------|-----------------|------------------------|----------------------------|------------------|---------------------------------------|---------------------------------|
| Limpens / Europe [87] | Nested (50) | 1 mg | Follicular hyperplasia | 33 (7 - 78) | 56 (9/16) | 1 - 100 | |
| | | | Reactive tonsils | 4 - 8 | 50 (4/8) | 1 - 1000 | |
| | | | Reactive nodes | ND | 0 (0/19) | ND | |
| | | | Normal marrow | ND | 0 (0/30) | ND | |
| Aster / USA [88] | Semi-nested (60) | 2 mg | Tonsils | 6.5 (2 - 32) | 25 (3/12) | 0.4 - 2.4 | |
| | | | Follicular hyperplasia | 34 (25 - 64) | 67 (2/3) | 0.5 - 4.6 | |
| Aster / Japan [88] | | | Tonsils | 6 (3 - 40) | 50 (5/10) | 0.3 - 60.2 | |
| Ohshima / Japan [89] | Single-step (ND) | ND | Reactive nodes | ND | 11 (2/18) | ND | |
| Liu / USA [90] | Nested (60) | 2 mg | Sorted PB B-cells | 50 (0 - 75) | 55 (29/53) | 0.8 - 32 | Frequency ∝ age |
| | | | Autopsy spleen | 50 (0 - 85) | 35 (11/31) | 2.7 - 853 | Liver + 1/10, other tissues neg |
| Bell / USA [91] | Nested (60) | 2 mg | Sorted PB B-cells | < 52 years | 48 (59/122) | ND | ↑ in smokers, no assoc. age |
| Limpens / Europe [92] | Semi-nested (56) | 1 mg | Sorted PB B-cells | ND | 67 (6/9) | ≈ 10 | |
| Ji / USA [93] | Semi-nested (46) | ≥ 7 mg | Normal PB | 6 - >60 | 63 (79/125) | 0.2 - 180 | Higher with age, M > F |
| Dolken / Europe [94] | Nested (60) | 0.01 - 1 mg | PB mononuclear cells | 38 (23 - 90) | 46 (26/57) | 1 - 100 | No assoc with age |
| Fusco / USA [95] | Nested (60) | 2.5 mg | PB lymphocytes | 27 (17 - 48) | 88 (30/34) | 0.08 - 960 | No assoc with age, M = F |
| Ranzly / Europe [96] | Semi-nested (70) | ~0.5 mg | Marrow | 68 (1 - 89) | 23 (11/48) | ND | Assoc with smoking |
| | | | PB | 70 (1 - 100) | 44 (60/137) | ND | No assoc age/sex/smoking |

finding a clear association ($r = 0.37$; $P < 0.0001$). Two of the negative studies were limited in size and power, with 57 and 34 patients only,^{94,95} but the large study of 137 patients by Rauzy *et al*⁹⁶ also failed to find any association between the incidence of positivity and age, although no estimate of the frequency of clonal cells was possible. In summary, one possible explanation for these observations is that while there may be no clear association between the actual rate of positivity for bcl-2 rearranged cells in the peripheral blood of normal individuals (using assays with sensitivities in the range of 10^{-5} to 10^{-6}) there does appear to be a reproducible association between the frequency of such cells with increasing age, at least over the age of 60. This explanation would also be consistent with the observation that using assays of greater sensitivity ($<10^{-7}$) almost all persons have detectable clonally rearranged cells (88%) regardless of age.⁹⁵

Gender: In all population-based series reported, there is a uniform gender imbalance in the frequency of follicular NHL, with males predominating. Similarly, in two of the four studies examining the relationship between gender and bcl-2 rearrangements in normal persons, males were more frequently positive.^{91,93} However, there is no intrinsic explanation for this gender imbalance and it may simply reflect a higher likelihood of exposure to other causative agents, such as tobacco, pesticides, or other environmental factors.

Smoking: The Bell study specifically addressed this issue, finding strong associations in multivariate analysis

between indices of tobacco use and the frequency of bcl-2 rearranged cells, whether this was measured by total pack-years ($P = 0.0004$), cigarettes smoked per day ($P = 0.008$), or total years of smoking ($P = 0.001$).⁹¹ Given the established epidemiologic link between follicular NHL and smoking discussed above, the large number of patients studied and thorough smoking history data obtained, this study strongly suggests a causative link between a substance contained within tobacco smoke and the generation of bcl-2 / IgH rearrangements within peripheral blood lymphocytes of healthy persons. Although not primarily designed to address this issue, and lacking data on translocation frequency, the Rauzy study also found a greater cumulative cigarette exposure among people with bcl-2 positivity in bone marrow samples (17.5 versus 4.0 pack-years; $P < 0.014$).⁹⁶

Geographic variation in bcl-2 rearrangements among normal persons and the incidence of NHL:

The next issue to be considered is whether these sporadic bcl-2 rearrangements detected in normal individuals have a similar locational clustering as is known to occur in patients with follicular lymphoma (see above). Firstly, all of the studies of normal individuals have been limited to exploration of the MBR region—there is no data available on the occurrence or frequency of bcl-2 rearrangements within the *mcr*. Further, it is important to recall that the PCR primers used in most studies also limit the region of the bcl-2 gene examined to the ~500 base-pair MBR region; thus it remains possible that there may be translocation events occurring at

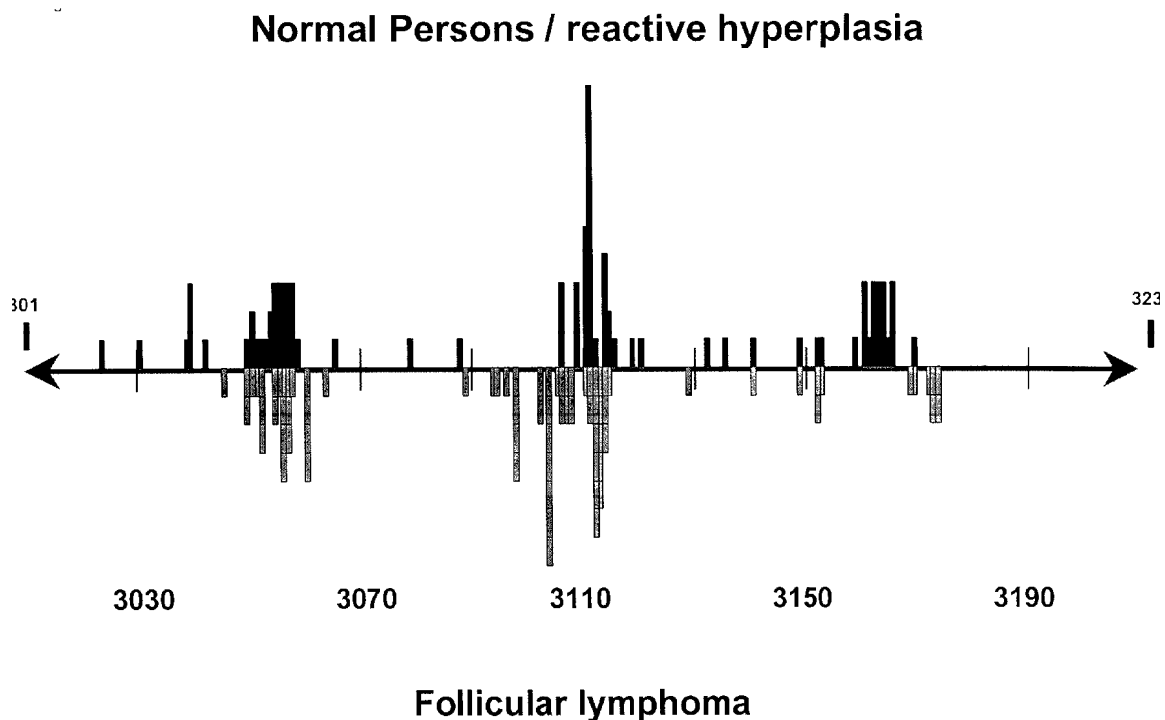


Figure 2: Comparison of breakpoint sites within MBR for bcl-2 gene rearrangements from normal individuals and follicular lymphoma. See text for details and references.

others sites within the *bcl-2* gene that have remained undetected by the methods employed to date. Even with these caveats, it is still of interest to compare the distribution of breakpoint sites within the 500 base-pair MBR among normal persons and from tumour samples of patients with follicular NHL. Such an analysis requires not just detection of a *bcl-2* gene rearrangement, but the generation of adequate PCR-product for full sequencing. This has been achieved and reported for 126 of the break-point sites in normal individuals^{88,92,94-96} and is compared with the break-point sites from 71 cases of follicular NHL (**Figure 2**).^{88 and references therein, 92,94-96} While there are minor discrepancies, such as a slight excess of breakpoints clustered in the area of base-pair 3165 among normal individuals (20% versus 7% among NHL) and a lower frequency of breakpoints in the area of base-pair 3105 among normals (12% versus 23%), the clear clustering in the regions of base-pairs 3055, 3100-3120, and 3165 are manifest (Figure 2). This is consistent with the premise that the translocations found in normal individuals may act as precursor lesions for the later development of follicular NHL.

If these sporadic *bcl-2* translocations found in normal individuals truly are the precursor lesions for later development of follicular NHL, their frequency may vary in geographic regions with different incidence patterns for follicular NHL. Unfortunately there is little data available on the frequency of such gene rearrangements in Asian populations. In the Aster study⁸⁸ 10 excised tonsils from Japanese persons were examined with five (50%) harbouring clonally rearranged cells. This was compared with the positivity rate of 33% (5/15) among similarly examined tonsils and follicular hyperplasia lymph nodes from American people. Although these numbers are very small, and from a single Asian ethnic group, they do suggest that these sporadic *bcl-2* gene rearrangements are not rare events among Asian people, and the lower incidence of clinically manifest follicular NHL is unlikely to be explained by a lower background rate of sporadic *bcl-2* gene rearrangement events.

There is more data available on the relative rates of positivity among European people, who have an intermediate incidence of NHL, and Americans (with a high rate). Restricting this analysis to those studies using methods of similar sensitivity,^{90-94,96} the cumulative incidence of detectable *bcl-2* gene rearrangements in the peripheral blood of Europeans is 45% (92/203) and among Americans is 53% (162/308) ($P = 0.12$). Allowing for differences in methodologic sensitivity between groups, and the inability to match for the age of subjects, gender distribution, and possible confounding factors such as smoking habits, there are no marked differences evident in the rate of detection of *bcl-2* rearrangements.

If we accept that the reported *bcl-2* rearrangements among normal persons are truly the precursor lesions for the subsequent development of follicular NHL, this similarity in the frequency of *bcl-2* rearrangements despite marked differences in the incidence of follicular NHL

strongly suggest that there are additional molecular events required subsequent to the acquisition of a clonal *bcl-2* / IgH rearrangement before a clinically evident follicular NHL develops. Further, it would appear that such later events, rather than the *bcl-2* rearrangements, are "rate limiting" for the development of clinical disease. Unfortunately, the nature of these additional events remain speculative, and the likely causative factors unknown. However, such a concept of the multi-step pathogenesis of follicular NHL is consistent with the observed pattern of cumulative genetic alteration with time among clinically evident follicular NHL, culminating in histologic transformation events. The above data suggest that a similar pattern of cumulative genetic alterations may be occurring during the initial phase of the natural history of the lymphoma.

Prognostic impact of *bcl-2* negativity:

The next issue to be considered is whether it is in fact necessary to eradicate all PCR-detectable *bcl-2* containing cells to attain long-term disease control or cure. From the above discussion, if it is possible for normal healthy persons to harbour "pre-lymphomatous" cells bearing clonally rearranged *bcl-2*, such cells may also be present in "cured" patients with follicular lymphoma. There is some data to suggest that this may indeed be the case. Even though the disease is clinically and radiologically "localized", the vast majority of patients with *bcl-2* rearranged stage I and II follicular lymphoma will have cells bearing the same *bcl-2* translocation as the diagnostic node biopsy detectable in the peripheral blood or bone marrow.^{80,97-99} After local radiation therapy, approximately 50% of these patients will be cured of their disease, with the risk of relapse diminishing greatly beyond 5 - 8 years. Although beyond this period of significant risk of relapse, approximately 25% of patients will still have detectable *bcl-2* rearranged cells in the peripheral blood using assays with sensitivity to the level of $\sim 10^{-5}$.^{80,100,101} With further follow-up of more than a year after initial detection of *bcl-2* rearranged cells, the majority of these patients remain in ongoing complete remission. These observations establish that eradication of PCR-detectable *bcl-2* rearranged cells is not absolutely required for long-term disease control, consistent with the hypothesis that some of these cells may actually be "pre-lymphomatous".

While attainment of PCR-negativity may not be an *absolute* requirement for long-term disease control, such a state of "molecular remission" may still be a useful surrogate marker of the eradication of those cells harbouring both *bcl-2*, and additional uncharacterised genetic abnormalities which have facilitated true malignant transformation. The first data supporting this premise came from the high-dose therapy studies of Gribben from Boston^{102,103} using immunologically purged bone marrow. These high-dose therapy studies will not be discussed in detail, but they are important as they raised the issue of the potential importance of attaining molecular negativity in the setting of conventional dose treatment.

Similarly, there is now data emerging that establishes

that the attainment of PCR-negativity is both a beneficial and achievable therapeutic goal for non-myeloablative therapies in advanced follicular NHL. López-Guillermo has recently presented outcome data from 194 patients with follicular NHL prospectively followed with serial PCR testing for bcl-2 in peripheral blood and bone marrow at the MD Anderson.¹⁰⁴ Even accounting for such potentially confounding factors as time-to-response, lead-time bias, baseline prognostic characteristics, and conventional response status, they observed a highly significant influence for the attainment of molecular remission on relapse risk ($P < 0.001$). For example, patients attaining a molecular remission within 12 months of starting therapy had a 76% failure-free survival at 4 years, compared with just 38% for those failing to achieve molecular negativity ($P < 0.001$). With further follow-up of this large cohort (median 4 years), these differences in relapse rate remain highly statistically significant, but there is still no clear difference in overall survival evident.¹⁰⁵ A preliminary analysis of a relatively small cohort of patients with localised disease, again by the MD Anderson group, suggests that attainment of molecular remission may also be of favourable prognostic impact.¹⁰⁶

If we then accept that attainment of PCR-negativity should be the therapeutic goal in patients with follicular NHL, what treatment strategies are available to achieve such a status?

Stage I / II: Standard therapy in such patients is still considered to be involved-field radiation therapy, which may deliver cure to as between 40% and 50% of patients. In an attempt to improve upon these outcomes, many centres are exploring the value of the addition of conventional alkylating-agent chemotherapy. There is little data yet available, but it is clear that both involved-field radiation therapy and combined modality treatment are able to attain molecular remission.^{97,106} Although considered a "local" therapy, radiation alone has been demonstrated to result in clearing of PCR-detectable clonal bcl-2 rearranged cells from the peripheral blood in one instance.⁹⁷ Such an observation suggests that bcl-2 rearranged cells in the peripheral blood may be "shed" from involved nodes, without necessarily indicating true disease dissemination. With combined modality treatment, the reported rate of molecular remission is 63% (15/24).¹⁰⁶ Previous phase-II data suggesting superior long-term outcome for combined modality therapy, together with this possibly increased rate of molecular remissions with combined modality therapy, provide the basis for an ongoing randomised Australian study of involved field radiation versus combined modality treatment. This study incorporates molecular monitoring and remains open for patient accrual.

Stage III: Although an uncommon clinical presentation, particularly with thorough morphologic bone marrow assessment, there are at least four reported single-arm studies demonstrating clearly that approximately 40% of patients with stage III follicular NHL can be cured with comprehensive lymphatic irradiation with follow-up beyond 20 years. This data alone confirms the need to separate stage

III patients from those with truly disseminated stage IV disease. As discussed for stage I/II disease, investigators have explored the additional benefit of adding alkylating-agent chemotherapy to comprehensive lymphatic radiation with a 5-10 year failure-free survival rate of 50%, marginally higher than anticipated for radiation alone. Further, it is significantly more difficult to deliver effective chemotherapy after such wide-field irradiation. Depending on the time-point examined, molecular remission is attained in 45-60% of patients following comprehensive lymphatic irradiation.¹⁰⁶ While intensive multi-agent chemotherapy (12 cycles of alternating CHOD-Bleo, ESHAP, and NOPP) can attain molecular negativity in 60-70% of patients with stage III disease, there may be reluctance to omit all radiation therapy in the absence of data demonstrating the curative potential for such chemotherapy regimens in patients with stage III disease. This question may eventually be answered by the randomised study of comprehensive lymphatic irradiation versus intensive chemotherapy ongoing at the MD Anderson.⁹⁷ There is no data available on the molecular remission rate with combined modality therapy in the setting of stage III disease.

Stage IV: Historically, the use of conventional alkylating agent or anthracycline-based chemotherapy schedules for advanced stage follicular lymphoma, while attaining conventional remission in more than 80% of patients, was rarely able to attain molecular negativity.^{85,93,108-110} Such observations have led to the investigation of alternative treatment strategies, searching for curative potential. Short of myeloablative strategies, there are two approaches demonstrated to have a reasonable likelihood of attaining molecular negativity, and these are being compared in an ongoing randomised study; the combination of fludarabine, mitoxantrone, and dexamethasone versus the alternative intensive schedule described above.¹⁰⁷ While both regimens are able to reproducibly achieve molecular negativity and a full analysis of outcomes is not yet available, the fludarabine combination does attain molecular negativity at an earlier time-point (82% versus 49% at 6-8 months; $P = 0.024$). Currently, there is no data available on the capacity of single-agent nucleoside analogues to attain molecular remissions in such patients, and randomised studies of single-agent and nucleoside combination therapies versus conventional alkylating agents are ongoing without yet revealing any overall survival advantage for either approach.

Other treatment approaches: One of the major steps forward in the management of follicular lymphoma in recent years has been the development and clinical application of monoclonal antibody therapies. The first of these to reach broad clinical application has been the chimeric mouse-human anti-CD20 antibody (Rituximab). When used as a single agent, Rituximab induces remissions in ~50% of patients with relapsed follicular NHL with a very favourable toxicity profile.¹¹¹ Preliminary analysis of patients treated with Rituximab have suggested that clearance of PCR-detectable bcl-2 rearrangements in the peripheral blood and bone marrow can be achieved with a very high frequency.¹¹²

This is a provocative observation, given that the majority of patients are considered to have partial remissions only by conventional response criteria, and that the median duration of these remissions is of the order of 12–14 months. Thus it would appear that the extremely favourable prognostic significance associated with chemotherapy-induced molecular remission may not necessarily be shared by antibody-induced remissions. A possible explanation for this is the preferential clearance of the particular compartment being sampled, rather than true eradication of all bcl-2 rearranged cells within the body; however, this is speculative. Regardless of these uncertainties surrounding the durability of antibody-induced molecular remissions, even transient attainment of molecular negativity in the peripheral blood and bone marrow may allow a window of opportunity for collection of uncontaminated progenitor cells for later use in supporting high-dose therapy programs; so-called *in vivo* purging.

Overview

Rather than presenting a schema for the current clinical management of patients with follicular NHL, the aim of this review has been to highlight unexplained variability in the incidence of follicular NHL and explore the potential role of known etiologic factors for follicular NHL in these differences. While it is clear that dysregulation of the bcl-2 oncogene plays a critical role in the pathogenesis of follicular NHL, consideration of the high frequency of development of clonal bcl-2 gene rearrangements in normal individuals, the similarity of the molecular character of these lesions, and the uniformity in the detection of such rearrangements over geographic regions with widely varying incidence rates for follicular NHL suggests that acquisition of a bcl-2 rearrangement is certainly not sufficient for subsequent development of follicular NHL and is probably not even rate limiting in the process. Further, the suggestion that follicular NHL among certain geographic region may have a lower frequency of bcl-2 gene rearrangements, coupled with the correlation of certain known epidemiologic risk factors with a higher rate of bcl-2 gene rearrangements among normal individuals, raises the possibility of separate and distinct etiologic paths for bcl-2 rearranged and bcl-2 germline forms of follicular NHL. Consistent with the premise of bcl-2 rearrangement occurring at an early and possibly “non-malignant” phase in the development of follicular NHL, it is clearly not essential to eradicate all PCR-detectable cells for clinical “cure”. However, while not essential, attainment of such “molecular remissions” has been shown to be associated with a favourable clinical outcome; thus it is reasonable to pursue such molecular remissions as a therapeutic goal in appropriate patients.¹¹³ Within this framework of understanding, currently available treatment strategies which are able to achieve this state of “molecular remission” in a high proportion of patients are discussed. However, it is important to remain aware that the range of available treatment strategies for patients with follicular NHL is expanding rapidly, and a genuine understand-

ing of the principles underlying the approach to treatment will be of far greater importance in the long-term than adherence to any one of the presently applied treatment regimens.

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