Dynamics of Cognitive Aging: Distinguishing Functional Age and Disease from Chronologic Age in a Population

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This paper introduces a methodological approach to the dynamics of cognitively normal (i.e., successful) aging compared with aging accompanied by different types of cognitive impairment and dementia. Using secondary analysis of a national representative database (Canadian Study of Health and Aging, 1991–1992), the authors show that the occurrence of an adverse event (symptom, sign, or disease), or the accumulation of a number of events, may be modeled as a logistic function of chronologic age in a population. In the cognitively normal, a linear relation between the logarithm of the odds of events and chronologic age was present for the majority of symptoms and signs. This regression represents the accumulation of each sign in a cognitively successful, aging population. The authors then estimated which ages for this cognitively unimpaired group correspond to the odds of the occurrence of symptoms found for a cognitively impaired population at any given chronologic age. This may be regarded as functional age, based upon the accumulation of a particular functional deficit in the impaired population, analogous to the concept of frailty. The dynamics of aging are a complex process of accumulation of deficits (morbidity), whereby decline from some previously healthy level of synergistically associated symptoms and signs results in distinct patterns of disease and staging. The modeling of these dynamics takes us a step further toward the definition and refinement of disease and normal aging. Am J Epidemiol 1999;150:1045–54.

aging; cognitive disorders; dementia; health; methods; morbidity; population

While aging is a universal experience, rates of aging are not uniform. Though this observation is commonplace, how to describe the process of aging and the heterogeneity of diseases, which are intricately woven into its fabric, is controversial (1–3). The adoption of frailty as a means of describing this heterogeneity (4) has created a fuzzy repository where the definition and operationalization of frailty (where made explicit) range from interacting dynamic models (5, 6) to specific associations with activities of daily living (7), metabolic imbalance (e.g., iron overload) (8), or strength gain (9).

A more precise method of describing the aging process and assaying the effects of diseases would be of value in the diagnosis and development of accurate therapeutics (10–17). It remains important to identify what successful or “normal” aging looks like in a wider context (18) and to see if it is possible to disentangle age-related processes from deficits with a distinctive disease etiology (19).

One method to study the process of aging is to examine the accumulation of deficits as they relate to the age of individuals in a population. Increasingly, there is recognition that decline does not follow a linear progression (20–23). Population heterogeneity results in variation in patterns of survival, as seen in crossover effects where, for example, the “advantaged” experience accelerated mortality in later years (24).

We recently addressed the issue of functional decline during Alzheimer’s disease and other dementias (25). Different diagnostic groups showed contrasting patterns of functional decline. Briefly, functional decline in dementia showed a log-normal distribution, whereas in those without cognitive impairment the distribution was exponential. We suggested that these differences reflect fundamental variation in the processes of functional decline between the two groups.

In this report, we extend that analysis to more precisely define the aging process by modeling the accumulation of deficits commonly associated with aging. To broaden the test of the concept of successful aging (26), we now compare the accumulation of specific patterns of functional symptoms between groups with...
and without cognitive impairment. In particular, we were interested to know whether the distinct patterns that we had observed between a diseased group and a normally aging group could be demonstrated when considering factors other than functional decline. We therefore investigated whether the pattern of accumulation of deficits showed distinctive profiles in different types of variables. These include deficits that occur even in normal aging, such as visual loss; those that occur in association with dementia, such as muscle rigidity or spasticity; and those that occur in age-associated disease states not usually associated with dementia, such as gastrointestinal complaints and skin problems.

MATERIALS AND METHODS

Sample

Between 1991 and 1992, a national cross-sectional, representative sample of Canadians aged 65–106 years standardized by age, sex, region, and type of residence (community or institution) was screened and then received an extensive clinical and neuropsychologic assessment (27). This resulted in diagnosis, using a standardized approach across the 18 study centers (28), of 921 people with no cognitive impairment, 861 with some cognitive impairment but no dementia (11), and 1,132 people with dementia. Alzheimer’s disease was diagnosed using NINCDS-ADRDA criteria (29). Vascular and other specific dementias and severity were diagnosed using criteria from the International Classification of Diseases, Tenth Revision (30).

Selection of symptoms and signs

In a secondary analysis of the clinical assessment database of the Canadian Study of Health and Aging, we identified a set of 22 symptoms, signs, and clinical conditions that target the loss of functional activities, sensory impairment, and general medical, health, and behavioral problems. Based upon clinical significance and analyses identifying signs that showed statistical variance among diagnostic categories, the following 22 symptoms and signs were selected: hearing disability, difficulty going out alone, chronic visual loss, difficulty with getting dressed, changes in sleep patterns, difficulty with cooking, abnormalities in limb tone, difficulty with toileting, palomental reflex abnormalities, difficulty with grooming, snout reflex abnormalities, diabetes mellitus, motor system resting tremor, skin problems, impaired vibration sense, hypertension, abnormal gait, cardiovascular problems, mobility impairment, urinary complaints, difficulty with bathing, and gastrointestinal complaints.

Analysis

Let $p_{ij}(T)$ be the probability that the $j$th symptom occurs among the patients from the $i$th diagnostic group at age $T$, where $i = 1, \ldots, n$; $n$ is the number of diagnostic groups; and $j = 1, \ldots, m$; and $m$ is the number of binary symptoms and signs. The odds of a particular symptom’s occurring in a specific diagnostic category are defined as a ratio, $p_{ij} / (1 - p_{ij})$. Each symptom or sign is either present, 1, or absent, 0, in the subject. For each symptom, the odds are estimated as a ratio of the sum of 1s to the sum of 0s, taking into account all subjects in the diagnostic group with age, $T$. When there were less than four subjects for a given age $T$, the odds were not calculated. We tested the hypothesis that the logarithm of the odds, $Y_{ij} = \log(p_{ij} / (1 - p_{ij}))$, is a linear function of age, $T$, that is, $Y_{ij} = b_0 + b_1T$. Linear regression techniques were applied to estimate the parameters of the linear model. In order to establish the significance of the correlation coefficient, $r$, Fisher’s $z$ transformation was calculated, $z = 0.5 \times \log((1 + r) / (1 - r))$. The Student $t$ criterion was used to establish the significance of the correlation coefficient, $r$: $t = z / (N - 3)^{1/2}$, where $N$ is the number of ages in that subsample. The significance level was set at $p < 0.05$.

Calculation of functional age

$T_c$ and $Y$ are the chronologic ages and corresponding logarithms of odds from the Canadian Study of Health and Aging database. A linear relation is established between the log(odds) for a sign and chronologic age: $Y^* = a + bT_c$, where $Y^*$ is the regression of the log(odds) for the group of subjects with chronologic age, $T_c$; $a$ and $b$ are least-square regression coefficients. Given chronologic age $T_c$, one can then estimate an average logarithm of odds $Y^*$ corresponding to this age. If this relation is statistically significant, we can invert the variables to estimate the age corresponding to a given log(odds). Hence, the average chronologic age $T_i$ for the cognitively successful aging subjects may also be calculated given the log(odds), $Y$: $T_i = c + dY$, where $c$ and $d$ are the regression coefficients ($c$ and $d$ can be expressed through $a$, $b$, and the correlation coefficient, $r$). Using this equation (derived from the normal group), we calculate the value of $T_i$ for the impaired group, given the log(odds), $Y$ for a certain chronicologic age, $T_c$. The slope of the functional age against the chronicologic age shows the rate of functional aging.

RESULTS

Accumulation of deficits in aging

Figure 1 shows that the proportion of subjects with impairment in mobility increases over time in the cog-
nively successful aging group, compared with those in the groups with cognitive impairment but no dementia and with dementia. This pattern holds for the majority of deficits. One can see the following: 1) progression of accumulation of the deficit with age for those with no cognitive impairment; 2) increasing accumulation of deficits with increasing cognitive impairment; and 3) increasing heterogeneity (wider variability) of accumulation of deficits with increasing cognitive impairment.

In order to characterize the relation of functional change with chronologic age, to heuristically illustrate what we describe here as functional age, we used the log(odds) of occurrence of a sign as a function of age for each of 22 deficits. For example, figure 2 illustrates the strongly significant correlation between the log(odds) for vision loss and age, calculated for each age between 65 and 98 years in the cognitively normal group, represented by solid circles ($r = 0.904$, $p < 0.0001$). The solid line is the regression of the log(odds) by chronologic age. Thus, the log(odds) calculated at a given chronologic age for the no cognitive impairment group (normal aging) correspond to the regression line, where the functional age coincides with the chronologic age. In contrast, the triangle ($\Delta$) identifies the log(odds) ($-0.43$) for this chronologic age, $T_c$ (73 years) among the cognitively impaired group. We then estimated the value of the corresponding chronologic age for the no cognitive impairment group (along the regression line), and this provided us with the functional age, $T_f$ (83.5 years). Figure 2 provides construct validity to the marked linear dependence of vision loss with age.

Variable relations between age and the accumulation of deficits

We calculated a "functional age" for each sign in those aging cognitively successfully and in those with dementia (a group that included people with mild, moderate, and severe Alzheimer's and vascular disease) as a function of chronologic age. Table 1 shows a significant linear increase for 16 of the 22 signs ($p < 0.05$) in the successful aging group. Although in each case the proportion of those who are cognitively impaired is higher than in those who are unimpaired, no significant age-dependent association appears for the ability to dress or to groom oneself. Additionally, there is no significant association for abnormality of limb tone, for the primitive neurologic palmomental and snout reflexes, and for the diseases of hypertension and diabetes. For two signs (difficulty with grooming and palmomental reflex), the relation between $T_c$ and $T_f$ was insignificant, although the correlation coefficient was higher than other deficits, as for some ages there were not enough available cases to calculate the odds.

Two broad patterns can be identified that characterize the relation between chronologic and functional age: 1) those deficits that are age related and 2) those that are not related to age. The age-related deficits can be identified by a significant correlation coefficient, $r$,
FIGURE 2. Defining functional age for vision loss in a national cross-sectional, representative sample of Canadians, 1991–1992. The dynamics of vision loss in the cognitively normal group are represented by the logarithm of the odds for vision loss as a function of age. Solid circles represent the logarithm of the ratio of the number of subjects with vision loss to the number of subjects without vision loss calculated at any age (log(odds)). The solid line shows a linear regression fitted by least squares. For the group with no cognitive impairment, therefore, functional age coincides with chronologic age. The correlation coefficient \( r = 0.904 \), and the number of distinct ages = 30. The triangle (△) identifies the log(odds) (-0.43) for this chronologic age, \( T_c \) (73 years), among the cognitively impaired group. We then estimated the value of the corresponding chronologic age for the non-cognitively impaired group (along the regression line), and this provided us with the functional age, \( T_f \) (83.5 years).

TABLE 1. Slopes (rates of the accumulation of deficits), standard error (SE), \( r \), and \( p \) for those aging with no cognitive impairment and those with dementia (Alzheimer’s disease and vascular disease) in descending order of strength of association

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Successful aging</th>
<th>Dementias</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>SE</td>
<td>( r )</td>
<td>( p )</td>
</tr>
<tr>
<td>Chronic visual loss</td>
<td>0.817*</td>
<td>0.073</td>
<td>0.904</td>
<td>0.000</td>
</tr>
<tr>
<td>Hearing disability</td>
<td>0.681*</td>
<td>0.088</td>
<td>0.823</td>
<td>0.000</td>
</tr>
<tr>
<td>Mobility impairment</td>
<td>0.573*</td>
<td>0.095</td>
<td>0.757</td>
<td>0.000</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>0.547*</td>
<td>0.094</td>
<td>0.739</td>
<td>0.000</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.516*</td>
<td>0.098</td>
<td>0.718</td>
<td>0.000</td>
</tr>
<tr>
<td>Vibration sense</td>
<td>0.486*</td>
<td>0.094</td>
<td>0.697</td>
<td>0.000</td>
</tr>
<tr>
<td>Difficulty bathing</td>
<td>0.362*</td>
<td>0.094</td>
<td>0.601</td>
<td>0.001</td>
</tr>
<tr>
<td>Difficulty cooking</td>
<td>0.266*</td>
<td>0.110</td>
<td>0.516</td>
<td>0.028</td>
</tr>
<tr>
<td>Difficulty going out</td>
<td>0.263*</td>
<td>0.101</td>
<td>0.513</td>
<td>0.017</td>
</tr>
<tr>
<td>Difficulty toileting</td>
<td>0.231*</td>
<td>0.108</td>
<td>0.480</td>
<td>0.050</td>
</tr>
<tr>
<td>Changes in sleep</td>
<td>0.207*</td>
<td>0.076</td>
<td>0.455</td>
<td>0.011</td>
</tr>
<tr>
<td>Difficulty grooming</td>
<td>0.193</td>
<td>0.093</td>
<td>0.439</td>
<td>0.052</td>
</tr>
<tr>
<td>Palomental reflex</td>
<td>0.175</td>
<td>0.085</td>
<td>0.415</td>
<td>0.054</td>
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<tr>
<td>Gastrointestinal</td>
<td>0.154*</td>
<td>0.088</td>
<td>0.393</td>
<td>0.031</td>
</tr>
<tr>
<td>Urinary complaints</td>
<td>0.152*</td>
<td>0.088</td>
<td>0.390</td>
<td>0.032</td>
</tr>
<tr>
<td>Skin problems</td>
<td>0.141*</td>
<td>0.065</td>
<td>0.376</td>
<td>0.040</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>0.129</td>
<td>0.075</td>
<td>0.360</td>
<td>0.099</td>
</tr>
<tr>
<td>Difficulty dressing</td>
<td>0.107</td>
<td>0.067</td>
<td>0.328</td>
<td>0.126</td>
</tr>
<tr>
<td>Snout reflex</td>
<td>0.064</td>
<td>0.054</td>
<td>0.253</td>
<td>0.256</td>
</tr>
<tr>
<td>Abnormal limb tone</td>
<td>0.059</td>
<td>0.056</td>
<td>-0.244</td>
<td>0.299</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.011</td>
<td>0.020</td>
<td>0.106</td>
<td>0.575</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.007</td>
<td>0.016</td>
<td>0.083</td>
<td>0.673</td>
</tr>
</tbody>
</table>

* Statistically significant value (\( p < 0.05 \).
in table 1. The strength of association of this age relation is expressed in terms of functional age, which identifies how it changes with chronologic age. In general, we see that dementia changes the trend in functional age. Two important patterns are revealed within those age-related deficits. Figure 3 shows that dementia weakens this trend but does not substantially affect the functional age. Functional age significantly increases with chronologic age in both those aging successfully and those with dementia. This is evident for vision and hearing loss and for gastrointestinal, skin, urinary, and sleep problems. In these cases we see some overlap between dementia and cognitively normal groups, a morbidity crossover effect where at some age the successfully aging become functionally older than those with dementia, although there is a wide standard error after this point.

Figure 4 illustrates a second pattern within the age-related deficits providing evidence that those with dementia are functionally older than those without dementia. The dementia and cognitively normal groups are distinct and no overlap appears. This pattern was found for mobility impairment; gait abnormalities; loss in activities of daily living such as bathing, toileting, cooking, and going out alone; and cardiovascular and sensory vibration problems. Further examination reveals that, in gait abnormalities, functional age significantly increases with chronologic age in both those aging successfully and those with dementia, but this relation may be attenuated by disease severity. In sensory vibration and mobility deficits, functional age significantly increases with chronologic age in those aging successfully but not in those with dementia.

Table 1 also identifies those deficits that show the second broad pattern: no age-related effects. There are no statistically significant trends in proportions of subjects with chronologic age for these signs, and for this reason functional age cannot be calculated according to our model. By considering proportions of subjects with the deficits, however, two patterns appear that differentiate those deficits not related to dementia (e.g., diabetes, hypertension) and those deficits that are associated with dementia (e.g., abnormal limb tone) (figure 5), snout reflex, palmomental reflex, resting tremor, and difficulty dressing and grooming oneself. There is considerable overlap in the proportion of subjects with cognitively normal aging and those with dementia for hypertension and diabetes (figure 6).

DISCUSSION

The dynamics of aging are a complex process of accumulation of deficits (morbidity) evidenced by a decline from some previous level of health. To develop this hypothesis, we began with an inductive method to compare the pattern of the accumulation of specific deficits in dementia and normal aging. We first compared the correlation between specific deficits and chronologic age and noted four broad patterns.

1. Age-related deficits in which at some point there is an overlap or crossover effect between the cog-

![FIGURE 3. Functional age dynamics for vision loss in a national cross-sectional, representative sample of Canadians, 1991–1992. ●, population with no cognitive impairment; △, population with dementia. Lines represent regressions, with slope, s.](image-url)
natively successful and dementia groups (e.g., vision, hearing, gastrointestinal, skin, urinary, and sleep problems).

2. Age-related deficits in which those with dementia are clearly functionally older and distinct from those aging successfully (e.g., gait and mobility problems, various activities of daily living, as well as cardiovascular and sensory vibration problems).

3. Non-age-related deficits with no association with dementia (e.g., diabetes, hypertension).

4. Non-age-related deficits associated with dementia (e.g., abnormality in limb tone, snout, and palmmontal reflex, resting tremor, and dressing).

A classic debate in gerontology is whether the effects of disease are separable from those of aging, and if they are, how such disentangling might proceed.

FIGURE 4. Functional age dynamics for abnormal gait in a national cross-sectional, representative sample of Canadians, 1991-1992. •, population with no cognitive impairment; Δ, population with dementia. Lines represent regressions, with slope, s.

70 80 90  
Chronological age, T (years)


(3). Using the Canadian Study of Health and Aging clinical database of elderly Canadians aged 65–106 years, this secondary analysis models the synergistic accumulation of cognitive and functional (physical) deficits in order to explore whether these represent disease or inevitable aging (10, 17, 18, 31, 32). Patterns were identified that characterize normal ("usual") or successful aging (26). We started with 22 deficits that provided a representation of medical, functional, and behavioral problems. Sixteen were found to be significantly correlated with age.

In previous reports we determined that significant dependencies between signs and symptoms successfully distinguish among the specific diagnostic subgroups for dementia (33, 34). In subjects without cognitive impairment, most of the deficits were found to be statistically dependent on each other (in what we defined as synergistic or antagonistic relations). A reduced number of dependent symptoms and signs were found, by comparison, in dementia patients. As the severity of dementia progresses, the dependence among these deficits weakens. Consistent with this weakening, we recently suggested a model of functional decline based on the assumption of independence of factors and demonstrated that the influence of separate symptoms and signs significantly exceeds the effects of interaction in functional decline (25). This report extends these findings further to characterize the dynamics of the aging process, as determined by the accumulation of medical, functional, and behavioral deficits. The process is clearly complex and dynamic, that is, the deficits group in nonrandom patterns (both synergistically and antagonistically), and shows distinct effects based on age, disease state, and their interaction.

There are important limitations to our study. Using a secondary analysis, we did not have available all the data we might have had. For example, there was no measure of heart rate variability, which has been proposed to serve as a prototype of the loss of complexity with aging (35, 36). In addition, there are few measures of variability and none that extend below the subject's age at assessment. Nevertheless, the database is rich with the important redundancies required for this type of modeling (33, 34).

The cross-sectional nature of our data introduces a survivor bias for all groups. A healthy participant bias, for example, may lead to an underestimate of the aging effect using these data. One limitation of the generalizability of these findings is our reliance on cognitive disorders as comprising the diagnosed group. While we recognize that there is much more to disease, and to frailty, than problems of the central nervous system, we chose to continue on this path for several reasons. It is a logical extension of the earlier work (12, 25, 33, 34). It allows us to work with a dataset in which cognitive problems have been well characterized. Furthermore, dementia is clearly associated with chronologic age, so that showing a distinct functional age is both more likely and potentially more important. In addition, while many factors are clearly associated with dementia, others clearly are not, so that we are able to test both convergent and divergent validity.

Moreover, we would like to note that the successful aging debate falls comfortably into the dementia dis-
course. It has been noted (37) that successful aging has shifted from “success” in the avoidance of disease and disability (38) to include the maintenance of physical and cognitive functioning, with a continuation of social and productive pursuits (26). Indeed, if Rowe and Kahn’s criterion of “physical functioning” is substituted for “social and occupational functioning,” the revised definition of success in aging mirrors that of the American Psychiatric Association’s definition of dementia (39).

Table 1 indicates that there are age-related losses, but in diseased patients, disease dominates the functional age insight. Figure 1 shows a clear demarcation among dementia, cognitive impairment but no dementia, and cognitively unimpaired groups, evidenced by impairment of mobility. While the middle ground held by cognitive impairment but no dementia provides construct validity for the emerging conceptualization of this diagnosis (11), the greater proportion and wider variability (heterogeneity) of accumulation of deficits in the dementia group also deserve some attention in keeping with our previous finding of synergistic breakdown with increasing cognitive decline (34). Again, we know that mobility is impaired in late Alzheimer’s disease and in vascular dementia with stroke. We suggest that, in the age-related deficits, vascular comorbidity in Alzheimer’s disease and the important role played by cerebrovascular disease in determining clinical symptoms of Alzheimer’s disease (12, 40) create a survivor effect among the “successful” aging. Simply, they live longer leading to greater deterioration in functional health, shown here by the steepness of the slope. These data appear to show a general “all states” worsening of health with dementia, which might be partially due to vascular effects on other organ systems and comorbid illness; that is, cerebrovascular disease does not occur in isolation but in the presence of other effects of atherosclerosis.

In figure 3, we provide evidence of morbidity crossover in later life. Incontinence or decubitus ulcers arising from immobility can well lead to deficits associated with later stage manifestations of dementia, providing one explanation for the morbidity crossover. Why this should occur in the case of vision or hearing problems is less obvious, although it may reflect apraxia or agnosia that has been misclassified. Further investigations of these observations will be undertaken. While mortality crossover is a well-accepted concept reflecting survivor effects (or simply misreporting) (24), the concept of morbidity crossover is less well developed. A crossover between what has been referred to as “advantaged” and “disadvantaged” groups allows speculation that further detailing of the dynamics of these deficits may provide clues to the delineation of late life expressions of genetic susceptibility factors (41) and/or environmental insults that occurred at a much earlier point in time (42–44). While extraneous and currently unknown factors may modify some genetically predetermined maximum life span, it might well be that we can establish personal biologic age based upon functional and cognitive capacities separate from chronologic age.

An interesting pattern was observed with respect to non-age-related deficits, for example, diabetes and hypertension. Although both illnesses are more common among older people, other effects predominate in the relation between disease and age. For example, the observation that the prevalence of diabetes at very advanced ages decreases (45) has also been documented in our population (46). Similarly, in hypertension, survivor effects operate so that its prevalence decreases beyond the age of 85 years (47). At late stages of dementia, blood pressure actually appears to decline (48).

We have also observed that some features were significantly related to age only in those with dementia. In addition to hypertension and diabetes, this occurred only in relation to abnormal limb tone. This last relation was very weak, however, and both its importance and interpretation remain unclear.

We have demonstrated that, even among age-associated illnesses, there are distinct patterns in the accumulation of specific deficits. Although, as Grimley Evans has put it, “... to draw a distinction between disease and normal ageing is to attempt to separate the undefined from the undefinable” (1, p. 40), these patterns conform, for the most part, to distinctions based on aging and disease. They also distinguish among types of diseases.

In general, we have demonstrated a relation between chronologic and functional age. This conceptualization of functional age also holds out the possibility of developing an index of personal biologic age. Moreover, the use of our model is not simply heuristic. This approach allows an estimate of the extent to which specific deficits are associated with a target condition, in this case, dementia. In consequence, we believe that this approach will have some value in helping to disentangle signs that are said to be antecedents to conditions such as dementia. We propose to test this hypothesis in the follow-up to the Canadian Study of Health and Aging.

ACKNOWLEDGMENTS

The study was supported by grants from the Novartis Foundation for Gerontological Research and the QEI...
Health Science Centre Research Foundation, Halifax, Nova Scotia. The data reported in this article were collected as part of the Canadian Study of Health and Aging, funded by the Seniors Independence Research Program, administered by the National Health Research and Development Program (NHRDP) of Health and Welfare Canada (project no. 6606-3954-MC[S]).

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