Objective: To evaluate diagnostic outcomes, especially as they relate to reason for referral, of patients referred to a university-based multiple sclerosis (MS) center for possible MS.

Methods: Retrospective medical record review of all new patient visits to University of Colorado Multiple Sclerosis Center, Denver, from January 1, 2001, to June 30, 2003.

Results: Of 281 patients referred to evaluate the possibility of MS, after initial review 33% were diagnosed with MS or possible MS by the McDonald criteria. The rest had other neurological conditions (31.5%), probable psychiatric diagnoses (22.5%), or no clear diagnosis was made (12.5%). Of patients with typical, possible, or atypical demyelinating syndromes, 71%, 27%, and 0%, respectively (P<.001), had MS or possible MS. Of the 63% of patients referred on the basis of clinical symptoms and signs, 46% were diagnosed with MS or possible MS vs 11% of patients referred primarily on the basis of abnormal brain magnetic resonance imaging (MRI) results (P<.001). Of patients referred because of abnormal MRI results who did not have MS or possible MS, 70% had a clear alternative etiology for the abnormal MRI results, including migraine, age older than 50 years, other neurological disease, or hypertension.

Conclusions: A significant percentage of patients referred to a university-based MS center have little or no likelihood of having MS, and many have undiagnosed, untreated psychiatric illness or common conditions with abnormal brain MRI results. With respect to the diagnosis of MS, greater training of primary care professionals, neurologists, and radiologists is necessary.

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METHODS

A comprehensive, retrospective medical record review was undertaken looking at a 30-month period from January 2001 through June 2003 for new patients seen by a single health care professional at the University of Colorado Multiple Sclerosis Center in Denver. Historical information was collected in a standardized fashion, with medical and neurological review of systems collected on the same checklists for the duration of the study period. The following observations were recorded: reasons for referral, initial neurological examination results, personal review of MRI and spinal fluid analyses, initial and final impressions, referral source, insurance status, and interpretation of the etiology of the MRI abnormalities. Patients were defined as having a syndrome typical of demyelination if they had symptoms and signs of optic neuritis (eg, painful visual loss with signs of optic neuropathy), a brainstem syndrome (eg, diplopia, vertigo, dysarthria), or a spinal cord syndrome (eg, weakness, bladder symptoms, and sensory level). Patients were defined as having possible demyelination if they had typical symptoms of demyelination but normal examination results or more vague symptoms potentially referable to central nervous system (CNS) demyelination (eg, paresthesias of the hand) and signs on examination consistent with this and not reflecting other disease (eg, not consistent with median neuropathy at the wrist). Patients were defined as not having a demyelinating syndrome of the CNS if the symptoms were all generalized (eg, fatigue, global weakness) or did not last at least 24 hours (eg, transient visual blurring for minutes) or signs on the examination reflected disease outside the CNS (eg, L5 radiculopathy).

Almost all patients were seen by another health care professional prior to our visit, usually a primary care physician and/or a neurologist, and all patients had at least 1 MRI of the brain performed at the request of the referring or another physician either prior to or after our first visit. Each MRI was formally reviewed by the examining neurologist (J.R.C.) at the time of the office visit, and that report was in a dictated note in the medical record. Specific details as to the number, size, shape, and location of the lesions, as well as intensity on T1-weighted imaging and enhancement after the injection of contrast material, were noted, as was a comment as to whether the MRI fulfilled criteria for MS, reflected an alternative disorder, or was nonspecific. All referral notes were reviewed and a determination made (prior to the data analyses) as to whether the referral to us was made primarily on the basis of the MRI report suggesting the possibility of MS. Patients were coded as having MS, possible MS (including a CIS), or no MS using McDonald criteria. Some patients were concluded not to have MS and had a definite diagnosis of another illness, while others were felt not to have MS and no clear diagnosis was made. A small number of patients were coded as not having a clear diagnosis, which would still include MS in the differential diagnosis. If another specific MRI sign (eg, stroke) was seen, it was coded by name. All T2 and fluid-attenuated inversion recovery white matter abnormalities that did not fulfill Barkhof criteria and for which no other specific etiology was identified were coded as “nonspecific.”

All statistical analyses were done using SAS version 8.0 (SAS Institute, Cary, NC). A χ² test was used where appropriate to examine for a potential association between study variables of interest using a P value of .025. This study was approved by the Colorado Multiple Institution Review Board.

RESULTS

Six hundred thirty-five new patient visits were scheduled during the defined study period. Forty-eight failed to arrive at their appointment, and 74 were scheduled for reasons unrelated to questions involving MS. The remaining 513 patients were referred to the clinic with a question related to MS (Table 1). The most common referral was for a primary or second opinion as to whether the patient had MS, constituting 281 (55%) of 513 referrals. The majority of the rest of the patients came with specific questions related to treatment options (immunotherapy or symptomatic) or because they wished or needed to change physicians (patient moved, doctor moved or retired, patient desire, insurance change).

DIAGNOSTIC CONFIRMATION OF MS

Among all 281 patients referred for a question of diagnosis of MS, 93 (33%) ultimately were diagnosed with MS or possible MS by the McDonald criteria (Table 2). Patients were categorized as to whether they had symptoms and signs typical of demyelination, possibly related to demyelination, or unlikely to be related to de-

<table>
<thead>
<tr>
<th>Reasons for Referral</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do I have MS?</td>
<td>281 (55)</td>
</tr>
<tr>
<td>MS/clinical</td>
<td>178 (33)</td>
</tr>
<tr>
<td>MS/abnormal MRI</td>
<td>103 (37)</td>
</tr>
<tr>
<td>Treatment options</td>
<td>92 (17.9)</td>
</tr>
<tr>
<td>Requesting new physician</td>
<td>85 (16.5)</td>
</tr>
<tr>
<td>Other (eg, research study question)</td>
<td>55 (10.7)</td>
</tr>
<tr>
<td>Total</td>
<td>513</td>
</tr>
</tbody>
</table>

Abbreviations: MS, multiple sclerosis; MS/abnormal MRI, patients referred almost exclusively on the basis of abnormal brain magnetic resonance imaging (MRI) findings; MS/clinical, individuals referred on the basis of clinical symptoms and signs, with or without abnormal laboratory results.

Main clinical question asked of all patients referred during 30-mo. study period.
myelination, and also as to whether they had abnormal neurological examination results referable to the CNS and demyelination. Of all patients diagnosed with MS or possible MS, 66% had typical signs of demyelination and a CIS, 34% had possible signs, and none had atypical manifestations. Among patients with typical demyelinating syndromes, 71% were diagnosed with MS or possible MS, compared with 27% of those with possible scenarios of demyelination ($P<.001$) and none of the patients with atypical scenarios ($P<.001$ for typical vs atypical and possible vs atypical comparisons). In those with atypical symptoms, 19% had abnormal neurological examination results and nearly all with abnormalities had only subjective abnormalities such as decreased sensation of light touch in a nonspecific distribution. Conversely, 98% patients with typical demyelinating syndromes had abnormal examination results ($P<.001$).

The majority of patients referred for a question of diagnosis of MS (178 [63%] of 281 patients) were referred to us on the basis of clinical syndromes, in the context of possibly abnormal laboratory study results. This group is referred to as “?MS/clinical” (Table 1 and Table 2). In a significant minority (103 [37%] of 281 patients referred for a question of diagnosis of MS), the possibility of MS was raised only on acquisition of a brain MRI revealing 1 or more T2 or fluid-attenuated inversion recovery lesions in the white matter. This latter group is referred to as “?MS/abnormal MRI.” Indeed, in this group, the referral often specifically and simply said “abnormal MRI, rule out MS.”

In the ?MS/clinical group, 77% of patients had typical (42%) or possible (35%) scenarios consistent with demyelination vs 59% in the ?MS/abnormal MRI group ($P=.005$). In the ?MS/clinical group, 63% had abnormal neurological examination results vs 35% in the ?MS/abnormal MRI group ($P<.001$). Of the ?MS/clinical patients, ultimately 46% were diagnosed with MS or possible MS vs 11% (12/103) for the ?MS/abnormal MRI group ($P<.001$). Five of these 12 patients had clinical scenarios highly typical of MS, and the other 7 had symptoms and signs possibly referable to MS. Thus, the MRI was highly unlikely to uncover occult MS in patients without signs and symptoms typical or at least suggestive of MS.

### ALTERNATIVE DIAGNOSES

Among patients in whom MS or possible MS was not diagnosed, a wide variety of alternative diagnoses (Table 3) was made, which accounted for the patients’ primary symptoms and signs. In 35 patients, no specific diagnosis could be made. Among those without MS were 63 patients in whom the examining neurologist felt there likely was a psychiatric cause (ie, somatoform disorder, mood disorder, anxiety disorder, or some combination of these) for patients’ symptoms and signs.

Of all patients referred primarily on the basis of MRI reports (103 patients) who did not have MS or possible MS (91 patients), nearly 70% had a clear alternative diagnosis or condition that explained the abnormal MRI findings (Table 4). For those without symptoms and signs of demyelination, more than 81% had an alternative diagnosis to explain the MRI changes and more than one third of these patients had a clinical diagnosis of migraine and a nonspecific brain MRI.

### REFERRAL SOURCES

Of all 513 patient referrals, 64% were from primary care physicians (including nurse practitioners and physician assistants), 25% were from neurologists, and 11% were from other physicians. Of all referrals for a question of MS (281 patients), more than half were made by primary care physicians and about one third by neurologists (Table 5). When comparing the ?MS/clinical group vs the ?MS/abnormal MRI group, there was only a slightly
greater number of referrals made by primary care physicians on the basis of abnormal MRI findings, and this difference was not statistically significant.

We do not know how many of the MRIs obtained by others were formally reviewed by the ordering physician. Thus, it is possible that a significant number of referrals may have occurred primarily or exclusively because of the interpretation on the official report. We asked if there was a relationship between training of the official MRI interpreter and whether the patient was referred primarily on the basis of the MRI report. Magnetic resonance images in the MS/abnormal MRI group were less likely to have been formally reviewed by a neuroradiologist and the reports were more likely to have suggested MS as a possibility than MRIs in the MS/clinical group, but neither of these differences were statistically significant (Table 6). The vast majority of reports in both categories, however, simply suggested MS was a possibility, as were other diagnoses such as vasculitis, small-vessel ischemic disease, and Lyme disease. It was no more likely for a report in either category to note lesions to be periventricular or distributed in a non-specific pattern, in spite of the fact that patients in the MS/clinical group were more than 4 times more likely to be diagnosed with MS or probable MS. Not 1 report referred to any of the published criteria for a radiological diagnosis of MS.

**COMMENT**

During a 30-month period, more than half of all new patient referrals to our university-based MS center asked for an opinion as to whether the patient had MS. This is a very different question than “What percentage of patients with a CIS go on to have MS?” Although this study assesses only the outcomes after an initial evaluation, many of these patients had symptoms for many years prior to arrival at our clinic. After the initial evaluation at our center was completed, only 33% of patients were confirmed to have MS or possible MS. Although the percentage might be greater with longer follow-up, what is most notable is that more than 30% of patients had only vague symptoms or symptoms not typically associated with MS (eg, headache), and the likelihood of diagnosing MS or possible MS after the initial visit with such symptoms was negligible (actually zero). In addition, just 13% of patients with normal examination results ultimately were diagnosed with MS or possible MS. Thus, atypical history and normal neurological examination results were highly predictive of not diagnosing MS.

The possible diagnosis of MS was raised in a significant minority of our referrals only after receipt by the referring physician of a report of abnormal MRI results of the brain. Only 11% of these patients were diagnosed with

### Table 3. Alternative Diagnoses for Patients Without Multiple Sclerosis or Possible Multiple Sclerosis*

<table>
<thead>
<tr>
<th>Alternative Diagnoses</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other neurological disease</td>
<td>88</td>
</tr>
<tr>
<td>Migraine</td>
<td>25</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>6</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>4</td>
</tr>
<tr>
<td>Cervical stenosis</td>
<td>4</td>
</tr>
<tr>
<td>Nonspecific headache</td>
<td>4</td>
</tr>
<tr>
<td>ADEM</td>
<td>4</td>
</tr>
<tr>
<td>Radiculopathy</td>
<td>3</td>
</tr>
<tr>
<td>CTS</td>
<td>3</td>
</tr>
<tr>
<td>BET</td>
<td>3</td>
</tr>
<tr>
<td>PAPS</td>
<td>2</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>2</td>
</tr>
<tr>
<td>Atypical facial pain</td>
<td>2</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>2</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic abnormality</td>
<td>2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2</td>
</tr>
<tr>
<td>Lumbar stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>1</td>
</tr>
<tr>
<td>Frangible</td>
<td>1</td>
</tr>
<tr>
<td>MSA</td>
<td>1</td>
</tr>
<tr>
<td>Scleritis</td>
<td>1</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>1</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>1</td>
</tr>
<tr>
<td>Fistula</td>
<td>1</td>
</tr>
<tr>
<td>Perry-Romberg</td>
<td>1</td>
</tr>
<tr>
<td>Ulnar neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>1</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Toxic drug effects</td>
<td>1</td>
</tr>
<tr>
<td>Cervical spondylosis</td>
<td>1</td>
</tr>
<tr>
<td>Postconcussive</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
</tr>
<tr>
<td>Possible psychiatric disease</td>
<td>63</td>
</tr>
<tr>
<td>Unclear diagnosis</td>
<td>35</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>186</strong></td>
</tr>
</tbody>
</table>

Abbreviations: ADEM, acute disseminated encephalomyelitis; BET, benign essential tremor; CTS, carpal tunnel syndrome; MSA, multiple system atrophy; PAPS, primary antiphospholipid antibody syndrome.

*Alternative diagnoses for all individuals evaluated for possible MS, in whom MS or possible MS was not sustained. Seven patients had 2 alternative diagnoses. Patients with migraine were listed here only if this was the main diagnosis and the primary symptom for which the patient sought neurological consultation. Patients with optic neuritis and transverse myelitis had remote, isolated neurological illness and no recurrence over many years.

### Table 4. Etiology of T2 or Fluid-Attenuated Inversion Recovery (FLAIR) Lesions Other Than Multiple Sclerosis or Possible Multiple Sclerosis*

<table>
<thead>
<tr>
<th>Etiology of T2 or FLAIR Lesions</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite migraine</td>
<td>34 (37)</td>
</tr>
<tr>
<td>Age-related</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Other neurological disease</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Nonspecific headache</td>
<td>7 (8)</td>
</tr>
<tr>
<td>No cause identified</td>
<td>20 (22)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>91</strong></td>
</tr>
</tbody>
</table>

Abbreviation: MRI, magnetic resonance imaging.

*Presumptive etiology of abnormal T2 or FLAIR lesions on brain MRI in patients without multiple sclerosis in whom the diagnosis was raised as a possibility after review of the initial brain MRI. Migraine is listed for all cases in which it was the etiology for abnormal MRI results, including those when the patient was referred with migraine as the main neurological symptom and those in whom it was a secondary symptom.
MS or possible MS, and all of the diagnosed patients had symptoms consistent with MS. The vast majority of those not diagnosed with MS or possible MS had clear other causes for the T2 hyperintense lesions seen on the MRIs. Thus, although MRIs are extremely useful in confirming the diagnosis of MS, defining risk of MS in patients with a CIS, and, partly, in assessing the prognosis of MS, they very rarely, if ever, uncover occult MS in patients with atypical neurological symptoms and signs. In this regard, MRI reports appear to be generating a significant number of referrals in patients with a very low likelihood of MS. This may be in part due to the actual interpretation, including listing MS as a possibility when there are any nonspecific abnormalities noted in the white matter. In addition, although we did not prospectively analyze this, it has been our experience that lesions are frequently referred to as periventricular in location and thus suggesting MS when, in fact, the lesions are simply subcortical. Thus, accuracy in the reports might be helpful in reducing unnecessary visits to an MS specialist and the anxiety associated with this possible diagnosis.

We also document a significant number of patients (22.5%) referred to us for MS who appear to have as the explanation for their symptoms 1 or more psychiatric disorders. These patients will be reported in detail in a separate article. These patients often go from physician to physician, using significant resources, not getting appropriate evaluation and treatment, and undergoing great emotional distress. The percentage of patients with possible primary psychiatric diagnoses in our population is similar to the percentage of patients with pseudoseizure seen in a comprehensive epilepsy center, consistent with the idea that psychiatric illness may be manifested in multiple neurological patterns and at a relatively high rate. From the point of view of MS, the vast majority of these patients had atypical clinical syndromes, not suggestive of MS, and normal or nearly normal examination results from a neurological perspective. Where examination abnormalities were discovered on elemental neurological examination, many were of the sort generally regarded as “psychogenic” or “pseudoneurological” in character. Most common in this regard was breakaway, or giveaway, weakness in a diffuse pattern not consistent with a CNS lesion. Some of these patients were referred on clinical grounds and some because of MRI reports but none had MS.

This is a retrospective study and has all the limitations of such a study. Although we made the distinction of “referred primarily on the basis of MRI” prior to our analysis of symptoms and diagnosis, there may be inherent biases in making the determination, and the true reason for referral may be somewhat unclear in some cases. There was no diagnosis made in 13% of patients, some of whom may ultimately be diagnosed with MS. The MRIs were reviewed at the time of the office visit by a neurologist with extensive expertise in the evaluation and care of patients with MS, including MRI review, but not by a blinded neuroradiologist. Because these patients were all referred to a single health care professional at a university-based center, their clinical scenarios may well not reflect those seen in a more general neurological practice and may reflect idiosyncrasies of referral patterns in Colorado.

Table 5. Referral Patterns*

<table>
<thead>
<tr>
<th>Category</th>
<th>PCP</th>
<th>Neurologist</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>?MS/Clinical</td>
<td>97</td>
<td>59 (33)</td>
<td>22 (13)</td>
<td>178</td>
</tr>
<tr>
<td>?MS/Abnormal MRI</td>
<td>65</td>
<td>31 (30)</td>
<td>7 (7)</td>
<td>103</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>90 (58)</td>
<td>29 (10)</td>
<td>281</td>
</tr>
</tbody>
</table>

Abbreviations: Other, other physicians; PCP, primary care physician (includes internal medicine and family practice physicians, physician assistants, and nurse practitioners); ?MS/abnormal MRI, patients referred almost exclusively on the basis of abnormal brain magnetic resonance imaging findings; ?MS/c clinical, individuals referred on the basis of clinical symptoms and signs, with or without abnormal laboratory results.

*Referral patterns for patients in whom we were asked to render an opinion as to whether they had multiple sclerosis. Values are expressed as number (percentage) of patients.

Table 6. Radiology Report*

<table>
<thead>
<tr>
<th>Category</th>
<th>?MS/Clinical, %</th>
<th>?MS/Abnormal MRI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroradiologist read</td>
<td>63</td>
<td>47</td>
</tr>
<tr>
<td>Periventricular lesions noted</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>MS/demyelination listed as possible</td>
<td>42</td>
<td>79</td>
</tr>
<tr>
<td>MS listed as likely</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Defined as nonspecific</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>No. of reports available</td>
<td>59</td>
<td>68</td>
</tr>
</tbody>
</table>

Abbreviations: MS, multiple sclerosis; ?MS/abnormal MRI, patients referred almost exclusively on the basis of abnormal brain magnetic resonance imaging findings; ?MS/c clinical, individuals referred on basis of clinical symptoms and signs, with or without abnormal laboratory results.

*Characteristics of formal brain MRI reports and readers in patients referred for a question of MS based on clinical symptoms vs interpretation of a brain MRI report.

Regarding the psychiatric possibilities raised here, there was no formal, prospective neuropsychiatry evaluation, and specific questioning related to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision categories was not done during the interviews. A better understanding of this patient group with regard to the presence or absence of diagnosable psychiatric conditions, as well as the types and frequencies of any such conditions, may be amenable to investigation using the method of retrospective medical record review. The clinical impression of the neurologist evaluating these patients clinically is that many, based both on clinical manifestation and history, appeared to have somatoform disorders, mood disorders, anxiety disorders, or some combination of these. However, formal evaluation of this group is needed and will be reported in a separate analysis in the future.

Medicine continues to rely on the art of differential diagnosis, and that art is an essential element of the evaluation of persons with possible diagnoses of MS. This complex neurological condition may manifest in a variety of ways and may be difficult to distinguish from other medical, neurological, and neuropsychiatric illnesses. A recent report found patients with MS had an average delay in diagnosis of 3.5 years, and this especially was a problem for patients with early, nonspecific sensory symptoms. Studies published when MRIs were just beginning to be used identified a variety of neoplastic, structural, and vascular lesions that mimicked MS. Indeed,
Rudick et al reported 10 patients who fulfilled formal diagnostic criteria for MS, yet had certain “red flags” that suggested a reevaluation and subsequent alternative diagnosis. In many of these patients, MRI vastly improved diagnostic acumen.

Poser was one of the first to note a significant number of misdiagnoses of MS potentially linked to overreliance on MRI. Of 366 patients diagnosed with MS by a board-certified neurologist, clinically definite MS was only confirmed in 65%. Many of the patients may have had what we now refer to as a CIS, or possible MS, but 24% had chronic fatigue syndrome or a psychiatric disorder. Our findings are consistent with those offered by Poser and emphasize that physicians should evaluate the possibility of MS based on the strength of the clinical history and examination and that MRIs should be obtained in the service of determining whether there is neuroradiological evidence supportive of that clinical diagnosis. Given the very low rate of MS diagnoses in the setting of abnormal MRI results without strong clinical history or examination findings, physicians are probably well-advised to consider other diagnoses besides MS in these contexts even when that issue is raised in neuroradiological reports. In short, MRIs are not a substitute for a good history and neurological examination in the diagnosis of MS.

Our findings—and particularly the low rate of MS in the setting of only abnormal MRI results as well as the relatively high rates of suspected psychiatric illness—also suggest that additional training regarding the clinical and neuroimaging manifestations of MS in the several fields of medicine involved in the initial evaluation of such patients may be needed. Family practice and internal medicine residencies have no such requirements, and the neurological training offered by many medical schools may not be sufficient to provide graduating physicians with expertise sufficient to this task. There is often little formal psychiatry and only variable neuroradiological training within neurology programs, but as of July 2004, an equivalent of 1 month of psychiatry training is required for neurology residents. It is not clear what other specific steps might be made to address these educational objectives, especially in the context of shorter work hours of resident trainees as of July 2003.

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REFERENCES