TWO YEARS AGO one of us received a call from a pediatrician concerning a 3-year-old Jewish child with asymptomatic splenomegaly. The diagnosis of Gaucher disease was suspected, and he had heard that the diagnosis could be established enzymatically from a blood sample. We assured him that this was, indeed, quite simple to do. The next day we received a blood sample, and the following morning called the pediatrician to congratulate him on his clinical diagnosis: the child did have Gaucher disease. "I know," he said, and then we learned to our dismay that he had proceeded to perform a marrow examination on his luckless patient. Just a few months ago we saw another child who had been diagnosed by marrow examination, which had then been followed by bilateral iliac crest biopsies and a liver biopsy "to establish the extent of the disease."

In 1967 Kampine et al. showed that the enzymatic defect in Gaucher disease was expressed in leukocytes, and it has been 20 years since we first described a simple and practical means for the diagnosis of Gaucher disease by assaying the acid β-glucosidase activity of the white blood cells5,7 (Fig 1). The validity and utility of this approach was confirmed by many other investigators over the next decade.4,9 The test is quite simple: leukocytes are separated from venous blood, incubated with a commercially available fluorescent substrate, and the fluorescence is measured in an ordinary filter fluorometer. The test is available in several laboratories in different parts of the country. Not only is it not traumatic to the patient, but it is more accurate and less costly than marrow examination.

Are, then, the examples of the wanton use of marrow examination to establish a diagnosis of Gaucher disease cited above exceptions? Unfortunately they are not. We have now reviewed the histories of 55 unrelated patients with type 1 Gaucher disease, almost all of whom we have seen personally (Table 1). Marrow examination was performed in 50 cases, often more than once. In 20 of these patients the marrow examination was performed without the diagnosis of Gaucher disease having been seriously entertained; in 27 cases the diagnosis was strongly suspected and marrow examination was nonetheless performed. Most of these marrow examinations were performed after 1972, when the technology required to make the diagnosis from a blood sample was well-established. In only two patients had the diagnosis been established only on the basis of leukocyte β-glucosidase activity. In one case marrow examination was performed by an internationally renowned hematologist, and the diagnosis...
of Gaucher disease was still missed. (Unfortunately the marrow films, now more than 25 years old, are no longer to be found.) In at least 10 relatives of patients with Gaucher disease marrow examinations were performed to determine whether or not the disease was present. In one of these instances, infant twins of a mother with Gaucher disease were subjected to marrow examination rather than being screened by enzymatic assay, which later also proved to be normal.

We performed \( \beta \)-glucosidase assays on the leukocytes of most of these patients. The results are shown in Fig 2. It is obvious that every case could clearly be diagnosed by performing this determination.

Is marrow examination ever justified in patients with Gaucher disease? There is an extremely rare phenocopy of Gaucher disease that is caused by deficiency of an activator of \( \beta \)-glucosidase rather than a deficiency of the enzyme itself. Only two such patients have ever been detected, none in the Jewish population. The existence of this rare deficiency state can hardly be considered justification for performing marrow examinations when the diagnosis of Gaucher disease is suspected. Indeed, as mentioned previously, marrow examination may lead to errors in the diagnosis of Gaucher disease, both in terms of the disease being overlooked, as indicated above, and in the existence of pseudo-Gaucher cells that lead to a mistaken diagnosis. Occasions certainly arise when marrow examination is useful, but these are rarely, if ever, present at the time of original diagnosis. Patients with Gaucher disease develop, probably with a higher incidence than the general population, various hematologic disorders, including chronic lymphocytic leukemia, multiple myeloma, lymphoma, and various leukemias. Under these circumstances marrow examination may be extremely helpful.

At one time it was believed that heterozygotes for Gaucher disease might be detected by the identification of occasional Gaucher cells in the marrow. Fortunately, this myth has died out and we no longer see relatives of patients with Gaucher disease subjected to marrow examination in the vain hope that their carrier status might be established by this means. Carrier detection is possible, but, as is shown in Fig 1, there is overlap between the \( \beta \)-glucosidase activity of the leukocytes of putative normal subjects and obligate heterozygotes. Although several modifications of our original method have been claimed to improve the ascertainment of heterozygotes, examination of the data show that the same or even greater degrees of overlap are present regardless of the technical details of the method used. Some improvement can be achieved by separating monocytes from lymphocytes in the Hypaque-Ficoll interface layer used for assay. The identification of the common mutations that cause Gaucher disease has recently greatly improved the accuracy with which the heterozygous state may be established, particularly when the mutations of the propositus have been identified. In Jewish patients about 75% of the Gaucher disease-producing alleles are those with a mutation at nucleotide 1226. This mutation can be detected relatively readily using "color PCR," a technique for detection of mutations recently introduced by Chehab and Kan. Combining this technique with enzyme assays has now made diagnosis of the carrier state for Gaucher disease much more accurate than was previously possible.

Hematology has its roots in morphology. It is understandable, from this point of view, that hematologists persist in considering the diagnosis of Gaucher disease a morphologic one. However, the advances in knowledge in this field have been such that the performance of marrow examination for the diagnosis of this disorder can no longer be justified by any standard.

**Table 1. Method of Diagnosis of 55 Patients With Gaucher Disease**

<table>
<thead>
<tr>
<th>Diagnosis by bone marrow</th>
<th>Pre-1972</th>
<th>Post-1972</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis suspected</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Diagnosis unsuspected</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Unsure</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diagnosis by hepatic or splenic histopathology</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diagnosis by leukocyte ( \beta )-glucosidase</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>20</td>
<td>35</td>
</tr>
</tbody>
</table>

**Fig 2.** Leukocyte \( \beta \)-glucosidase activity of the lymphocyte/monocyte layer obtained after Ficoll-Hypaque separation of the white blood cells from 42 patients with Gaucher disease and 17 normal controls. In each case the diagnosis could have been established by leukocyte \( \beta \)-glucosidase assay.

**REFERENCES**

3. Beutler E, Kuhl W: The diagnosis of the adult type of Gaucher's disease and its carrier state by demonstration of defi-
ciency of beta-glucosidase activity in peripheral blood leukocytes. J Lab Clin Med 76:747, 1970


