Cerebral Blood Flow Study in Patients with Moyamoya Disease Evaluated by IMP SPECT

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We studied the usefulness of IMP SPECT with acetazolamide in 16 patients with moyamoya disease. Cerebral angiography was performed for all patients who were classified in three grades according to their angiographic stages. Methods: Techniques used included ring-type emission computed tomography with a minicomputer system. Patients received 111 MBq of \textsuperscript{123}I-IMP and SPECT images were obtained 20 min postinjection. Nine patients were studied using iodoamphetamine (IMP) SPECT with and without acetazolamide. IMP SPECT with acetazolamide was performed 20 min after each injection of 1 g of acetazolamide. Results: Low perfusion areas in the upper and lower frontal, parietal and temporal regions in grades 2 and 3 using IMP SPECT were observed. The mean cerebral-to-cerebellar activity ratios (C/C ratio) of six regions (upper and lower frontal, temporal, parietal occipital and basal ganglia) in grades 1, 2 and 3 were 0.96 to 1.06, 0.91 to 0.96 and 0.76 to 0.88, respectively. Conclusion: Our results indicate that measurement of regional cerebral blood flow (rCBF) elucidates cerebral hemodynamic factors, including the reactivity of cerebral vessels which cannot be detected angiographically in patients with moyamoya disease, and that the acetazolamide test is useful for detecting cerebral blood flow reserve. The test can be used to detect disease progress prospectively.

Key Words: Iodoamphetamine; moyamoya disease; cerebral blood flow


SPECT imaging of the brain with N-isopropyl-p-[\textsuperscript{123}I] iodoamphetamine (IMP) reflects regional cerebral blood flow (rCBF) and has become a routine diagnostic procedure for cerebrovascular disease, brain tumors, dementia and other diseases of the brain. Its clinical usefulness in these etiologies has been reported elsewhere (1–6).

Moyamoya disease is a cerebrovascular disorder involving the distal portion of the internal carotid artery with basal telangiectasias comprising dilated collateral leucostriate and thalamoperforating arteries (7). The abnormal findings of rCBF images are usually larger than regions of low density lesions observed in computed tomography (CT), and the clinical usefulness of rCBF studies by PET or SPECT in patients with moyamoya disease has also been reported (8,9).

Acetazolamide is a vasodilative agent which causes increases of regional blood flow in normal tissue and in ischemic regions supplied by a stenotic artery which reacts to acetazolamide. However, this agent cannot produce effects in an ischemic region where an artery does not react with acetazolamide. Therefore, these regions appear as relatively low perfusion areas compared to areas of normal tissue and ischemic regions which react to acetazolamide (10–17). The acetazolamide test is a useful method for detecting affected regions because of better discriminative images between normal and ischemic lesions. Its usefulness has been reported in patients with cerebroocclusive disease (12–15); however, clinical application of IMP SPECT with the acetazolamide test in moyamoya disease has not yet been reported. We describe the usefulness of brain SPECT in patients with moyamoya disease and discuss the clinical usefulness of the acetazolamide test for detecting the reactivity of cerebral blood vessels.

MATERIALS AND METHODS

Patient Selection

Data were acquired for 9 normal controls and 16 patients (7 males and 9 females) who had moyamoya disease and who presented with ischemic symptoms. The patients' mean ages were 16.7 yr ± 11.2 yr (mean ± s.d.). Moyamoya disease was diagnosed by cerebral angiography in all patients as proposed by Suzuki et al. (7). IMP SPECT was also performed on normal controls in three different age populations. They had both CT examinations and IMP SPECT because of abnormal EEGs after head trauma or clinical symptoms such as epilepsy, where IMP SPECT and CT showed normal findings.

IMP SPECT Procedures

A ring-type emission computed tomograph (SET-031, Shimadzu Co., Kyoto, Japan) and a minicomputer system (ECLIPSE S-120, Nippon Datageneral Co., Tokyo, Japan) were used. The camera consisted of a gantry assembly with 64 scanning detectors. This system had three rings and simultaneously acquired 12 parallel slices with a center-to-center interslice distance of 1.7 cm. A high-resolution collimator was used. Iodine-123-IMP (111 MBq) was injected intravenously and SPECT images were obtained 20 min postinjection. In each slice, 600 kcts were acquired. Acquisition times were 15–20 min. The raw data were reconstructed by...
filtered backprojection using a 64 × 64 matrix with a Ramachandran-Butterworth filter with an order of 8 and a cutoff frequency of 28 mm. The full width at half maxim was 15 mm in the center of the gantry by phantom study.

**Data Analysis**

*Distribution of Low rCBF Areas.* Thirty-two hemispheres of 16 patients were classified in three grades according to angiographic stages as reported by Suzuki et al. (7). According to their reports, the angiographic findings of each stage are as follows:

- **Stage 1.** Narrowing of the carotid fork.
- **Stage 2.** Dilatation of the main intracerebral arteries. Moyamoya vessels are observed over the carotid fork.
- **Stage 3.** The deflection of the middle and anterior cerebral arteries. The moyamoya vessels are clearly demonstrated.
- **Stage 4.** Occlusion of the internal carotid artery extends as far as the junction of the posterior communicating artery, and finally, the posterior cerebral artery. The moyamoya vessels become rough.
- **Stage 5.** All of the main arteries arising from the internal carotid artery completely disappear. The moyamoya vessels are limited to the syphon and are minimized and have a tendency to be reduced.
- **Stage 6.** The syphon of the internal carotid artery disappears completely and the original moyamoya vessels are also completely missing. In addition to these stages, patients in the present study included stage 0 on right side in a case with unilateral moyamoya disease whose angiogram was normal on the right side.

Three groups are shown in Table 1. Mean ages of these three groups did not significantly differ (p > 0.05). IMP SPECT images were analyzed by two experienced observers without previous knowledge of angiographic stages.

*Cerebral-to-Cerebellar Ratios.* The circular ROIs were set on SPECT images in the upper and lower frontal, temporal, parietal and occipital regions, and the basal ganglia and cerebellar hemispheres (Fig. 1). The size of the ROI was 20 mm in diameter, and the mean values of two or three ROIs in six regions including the upper and lower frontal, temporal, parietal, occipital and the basal ganglia were calculated. Cerebral-to-cerebellar activity ratios (C/C ratio) were estimated by dividing counts in the regions by those in the cerebellum. Values were estimated as mean ± s.d. according to grade.

**C/C Ratios in IMP SPECT with the Acetazolamide Test.** IMP SPECT with acetazolamide was performed in nine patients. To obtain IMP SPECT with acetazolamide, images were obtained a second time within 1 wk after the first scan. The same dose of IMP was injected 20 min after intravenous injection of acetazolamide (1 g). Data acquisitions were done using the same instruments and procedures as those for IMP SPECT without acetazolamide.

**Statistics**

Data were reported as means ± s.d. Means for age groups were compared using the nonpaired Student’s t-test. The C/C ratios in six regions based on IMP SPECT images without acetazolamide were also compared using the nonpaired Student’s t-test. The paired Student’s t-test was used for comparing C/C ratios in six regions based on IMP SPECT images with and without acetazolamide.

**RESULTS**

*Distributions of Low rCBF Areas in IMP SPECT.*

The numbers of low rCBF regions in the 16 patients are shown in Table 2. The frontal and parietal lobes were the most affected areas, but low perfusion areas were observed in all of the anterior and posterior circulation regions, the numbers of which ranged from 4 to 9 out of 16 hemispheres. There was no laterality in the numbers of affected areas. Table 3 shows the distribution of low rCBF areas according to grade. In grade 1, low rCBF areas were not observed except for one parietal region on one side in one patient. In grade 2, from 3 (15.8%) to 8 (42.1%) of 19 hemispheres showed low rCBF, which was observed most frequently in the frontal region (42.1%) and less frequently in the basal ganglia (15.8%). In grade 3, low rCBF areas were observed in more than 5 (62.5%) of 8. The percentage of low rCBF areas increased in proportion to the severity of the respective grade.

**TABLE 1**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Angiographic stage</th>
<th>No. of hemispheres</th>
<th>Age (yr) (mean ± s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stage 0–2</td>
<td>5</td>
<td>21.2 ± 16.3</td>
</tr>
<tr>
<td>2</td>
<td>Stage 3</td>
<td>19</td>
<td>15.2 ± 9.2</td>
</tr>
<tr>
<td>3</td>
<td>Stage 4–5</td>
<td>8</td>
<td>17.5 ± 11.1</td>
</tr>
</tbody>
</table>

n = 16; number of hemispheres = 32.
TABLE 2
Distribution of Low rCBF Areas

<table>
<thead>
<tr>
<th>Area</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Upper</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Lower</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Temporal</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Parietal</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Occipital</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

n = 16; number of hemispheres = 32.

C/C Ratios In IMP SPECT

Tables 4 and 5 show estimates of mean C/C ratios in each region according to age and grades, respectively. There were occasional decreases according to age in normal controls, but these were not significantly different. In moyamoya disease, the mean C/C ratios ranged from 0.96 to 1.06 and from 0.91 to 0.96 in grades 1 and 2, respectively. The mean C/C ratios in grade 3 were relatively low (0.76–0.88) compared to those in grades 1 and 2. The C/C ratios in stage 2 were significantly lower than those in stage 1 in one (temporal) of six regions, and those in grade 3 were significantly lower than those in stage 2 in three (upper frontal, temporal and parietal) of six regions, and those in stage 3 were significantly lower than those in stage 1 in all regions. The mean values had a tendency to decrease as the stage of the groups increased.

C/C Ratios In IMP SPECT with Acetazolamide Test

Table 6 shows comparisons of the C/C ratios with and without acetazolamide among nine patients. In grade 1, the mean C/C ratios of IMP SPECT without acetazolamide did not differ significantly from those with the acetazolamide test. There were significant differences between the two C/C ratios in the upper and lower frontal, parietal and temporal regions in grade 2. Although most of the mean C/C ratios of IMP SPECT with acetazolamide were lower than those without acetazolamide in grades 2 and 3, there were no significant differences between the two C/C ratios of the basal ganglia and the occipital region in grade 2, and between the two C/C ratios of all six regions in grade 3.

TABLE 3
Distribution of Low rCBF Areas

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of hemispheres</th>
<th>Frontal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upper</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>6 (75%)</td>
</tr>
</tbody>
</table>

n = 16; number of hemispheres = 32.

Case Reports

Figures 2A and B show right and left cerebral angiogram from a 6-yr-old boy. He was admitted to our hospital because of transient ischemic attacks (TIAs) of aphasia and hemiparesis of the right upper extremity. Angiographic stages were grade 1 (Stage 1) on the right side and grade 2 (Stage 3) on the left side. Figure 2C shows IMP SPECT images without acetazolamide. Activities were slightly decreased throughout the entire left cerebral hemisphere. The C/C ratios ranged between 0.89 and 1.03.

Figure 2D shows results of IMP SPECT with acetazolamide in the same patient as was shown in Figure 2C. There was markedly decreased activity throughout the entire left cerebral hemisphere in comparison with IMP SPECT images without acetazolamide. The C/C ratios also decreased between 0.73 and 0.88, except for those in the occipital region.

Figures 3A and B show right and left cerebral angiogram from a 10-yr-old girl. She had been complaining of headaches and TIAs consisting of unconsciousness for 2 mo. The angiographic stages were grade 2 (Stage 3) on both sides. Figure 3C shows IMP SPECT without acetazolamide. Activity decreased slightly throughout the entire left cerebral hemisphere. The C/C ratios were between 0.73 and 0.80. Figure 3D shows IMP SPECT images with acetazolamide. There is decreased activity in the left and right frontal regions and in the left temporal region when compared with IMP SPECT images without acetazolamide. The C/C ratios also decreased between 0.58 and 0.64. Activity increased slightly in the left occipital region and in the left basal ganglia. The C/C ratios changed from 0.78 to 0.80 and from 0.73 to 0.83, respectively.

DISCUSSION

Moyamoya disease is a rare cerebrovascular disorder involving the distal portion of the internal carotid artery and/or the circle of Willis with basal telangiectasias comprising dilated collateral lenticulostriate and thalamoperforating arteries (7,8,18–20). The name moyamoya ("puff of smoke") was derived from the angiographic appearances of the cerebrovascular abnormalities of collateral vessels. The initial symptoms at onset are a neurological deficit which is caused by ischemic changes in the brain or by subarachnoid hemorrhage (21,22). The disease progresses...
slowly and there is no effective treatment. Moyamoya disease is diagnosed angiographically and follow-up examinations are necessary to evaluate disease progress. Although bilateral involvement by this disease is common, cases of unilateral involvement by moyamoya disease have also been reported (18). Our present study included one case of unilateral moyamoya disease.

The CT findings in this disease consist of low density regions which indicate brain infarction due to stenosis or obstruction of a cerebral artery (23). Frontal and parietal regions are frequently affected. Ischemic lesions on CT or MR images consist of cerebral infarction, brain atrophy and ventricular dilatation (24-28). In the present study, low rCBF areas were observed most frequently in the frontal and parietal lobes. However, the basal ganglia and occipital regions were involved less frequently. The abnormal findings of rCBF images are usually larger than regions of low density lesions observed in CT (27).

The C/C ratios of the regions decreased according to the grades, especially in the upper and lower frontal, temporal and parietal regions. Only the temporal region showed significant differences between the C/C ratios in grade 1 and those in grade 2. Three regions (upper frontal, temporal and parietal regions) showed significant differences between the C/C ratios in grade 2 and those in grade 3. All regions differed significantly according to the C/C ratios in grade 1 and those in grade 3. These results showed that the C/C ratios and grades correlate well in the peripheral regions supplied by the anterior and middle cerebral arteries, but that the posterior circulation regions, including the occipital region and basal ganglia, are less affected because these regions are supplied by branches of the middle and posterior cerebral arteries. These findings are compatible with data reported previously (8).

Kuwabara et al. (9) reported that the right side was involved more frequently than the left side in unilateral moyamoya disease, and that areas of low rCBF lesions on the right side were larger than those on the left side, even in bilateral moyamoya disease. However, there was no lateral predominance of affected areas in our study.

Denays et al. have reported that rCBF changes according to age (29). The C/C ratio is small in a 1-month-old baby, however, this ratio increased from age 2 mo to 1 yr; it then decreased slightly until young adulthood and decreased gradually thereafter. The change is small after 2 mo compared to before 2 mo of age. Our study included a 4-yr-old boy, but the other patients ranged in age from 6 to 46 yr. We think that there is little effect on C/C ratios by changing rCBF values due to aging when compared to individual differences as shown in Table 4.

Lassen et al. (11) reported the effect of acetazolamide on rCBF. Acetazolamide causes significant increase of rCBF, which reduces symptoms of acute mountain sickness. The usefulness of the acetazolamide test in cerebro-occlusive disease has also been reported (12-14). Vorstrup et al. reported that acetazolamide is valuable for detecting reduced rCBF reserve in patients with occlusive carotid disease (12). Acetazolamide is a vasodilator which offers the

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**TABLE 4**

C/C Ratios According to Age in Normal Controls

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No. of hemispheres</th>
<th>Frontal</th>
<th>Temporal</th>
<th>Parietal</th>
<th>Occipital</th>
<th>Basal ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 ± 1.5</td>
<td>4</td>
<td>1.04 ± 0.08</td>
<td>1.05 ± 0.10</td>
<td>1.09 ± 0.05</td>
<td>1.02 ± 0.06</td>
<td>1.00 ± 0.16</td>
</tr>
<tr>
<td>15.0 ± 2.9</td>
<td>6</td>
<td>0.98 ± 0.04</td>
<td>1.01 ± 0.08</td>
<td>0.99 ± 0.06</td>
<td>1.00 ± 0.06</td>
<td>0.97 ± 0.05</td>
</tr>
<tr>
<td>36.7 ± 11.5</td>
<td>8</td>
<td>0.95 ± 0.06</td>
<td>0.97 ± 0.03</td>
<td>1.01 ± 0.04</td>
<td>0.95 ± 0.06</td>
<td>0.94 ± 0.07</td>
</tr>
</tbody>
</table>

Values are means ± s.d.

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**TABLE 5**

C/C Ratios According to Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Frontal</th>
<th>Temporal</th>
<th>Parietal</th>
<th>Occipital</th>
<th>Basal ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper</td>
<td>Lower</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.03 ± 0.08*</td>
<td>1.03 ± 0.08*</td>
<td>1.08 ± 0.05*</td>
<td>0.98 ± 0.07*</td>
<td>0.95 ± 0.06*</td>
</tr>
<tr>
<td>2</td>
<td>0.92 ± 0.13**</td>
<td>0.90 ± 0.17*</td>
<td>0.96 ± 0.08*</td>
<td>0.95 ± 0.07*</td>
<td>0.91 ± 0.06**</td>
</tr>
<tr>
<td>3</td>
<td>0.88 ± 0.12**</td>
<td>0.85 ± 0.17*</td>
<td>0.79 ± 0.12*</td>
<td>0.76 ± 0.12*</td>
<td>0.84 ± 0.12**</td>
</tr>
</tbody>
</table>

* p < 0.05.
** p < 0.01.
*** p < 0.001.

Values are means ± s.d.
TABLE 6
C/C Ratios With and Without Acetazolamide

<table>
<thead>
<tr>
<th>Grade</th>
<th>Frontal</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper</td>
<td>Lower</td>
<td>Temporal</td>
<td>Parietal</td>
<td>Occipital</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td>Acetazolamide (−)</td>
<td>1.07 ± 0.07</td>
<td>1.07 ± 0.07</td>
<td>1.06 ± 0.03</td>
<td>0.95 ± 0.07</td>
<td>0.95 ± 0.03</td>
<td>0.98 ± 0.04</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0.96 ± 0.09&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.94 ± 0.07&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.97 ± 0.06&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.94 ± 0.06&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.91 ± 0.06</td>
<td>0.94 ± 0.08</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0.78 ± 0.14&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.80 ± 0.08&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.87 ± 0.05&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.75 ± 0.04&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.89 ± 0.05</td>
<td>0.89 ± 0.06</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1.03 ± 0.01&lt;sup&gt;t&lt;/sup&gt;</td>
<td>1.09 ± 0.02&lt;sup&gt;t&lt;/sup&gt;</td>
<td>1.05 ± 0.05&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.96 ± 0.06&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.97 ± 0.04</td>
<td>1.03 ± 0.06</td>
</tr>
</tbody>
</table>

<sup>t</sup>p < 0.05.<br> <sup>t</sup>p < 0.001.<br> Values are means ± s.d.

Convenience of intravenous administration with rapid onset of vasodilation. Maximum response occurs approximately 25 min postinjection and has a half-time of 90 min (15).

Acetazolamide studies in cases of normal vasculature demonstrate a range of increase of rCBF of 57%–70% (16). The possible mechanisms involved include inhibition of the enzyme carbonic anhydrase in the brain parenchyma, which causes acute decrease in pH. The effect of acetazolamide on rCBF is probably explained by a decrease in brain pH. Thus, acetazolamide causes an increase in rCBF without change of the flow distribution in normal subjects (16). Although acetazolamide can also cause increases of regional blood flow in the brain, it cannot cause such increases in blood supply in ischemic regions or even in normal regions where there are no cerebral blood flow reserves. Decreased reactivity to acetazolamide is thought to be due in large part to a decreased cerebral vascular reserve secondary to vasodilation in the resting state as a compensatory mechanism for proximal stenosis and/or occlusion (13). This results in relatively low activity regions compared to blood flow in normal tissue.

FIGURE 2. (A) Right and (B) left cerebral angiogram from a 6-yr-old boy. Narrowing of the right carotid fork is observed without stenosis or obstruction of the branches in the right anterior and middle cerebral artery. The defects of the middle and anterior cerebral arteries are observed in the left side. The moyamoya vessels are clearly demonstrated. The angiographic stages were Group 1 (Stage 1) on the right side and Group 2 (Stage 3) on the left side. (C) IMP SPECT image before acetazolamide. Activity decreased slightly in the entire left cerebral hemisphere. C/C ratios are between 0.89 and 1.03. (D) IMP SPECT image after acetazolamide. Activity decreased markedly in the entire left cerebral hemisphere. C/C ratios also decreased between 0.73 and 0.86, except for those in the occipital region.
The acetazolamide test can detect low rCBF reserve regions because of relatively high contrast images between normal or ischemic lesions with reactive vessels and those with no reactive vessels. Hyperventilation is also used to evaluate the cerebral blood flow reserve, because decreased PaCO₂ in the arterial blood after hyperventilation causes constriction of the cerebral artery (30). However, this procedure can be dangerous in some cases and it requires the patient's effort. Quantitative analysis of IMP SPECT is also difficult because the degree of decrease of rCBF depends on the degree of such effort by the patient.

In the present study, mean C/C ratios without acetazolamide in grade 1 were not changed after acetazolamide. The mean C/C ratios in grade 2 were lower than those in the upper and lower frontal, temporal and parietal regions after acetazolamide and they were statistically significant. This shows that cerebral vascular reserve in these four regions decreased in grade 2. There were cerebral vascular reserves in all six regions of grade 1 and in the occipital region and the basal ganglia in grade 2. These results indicate that perfusion in the posterior region and central region around the basal ganglia which are supplied by the moyamoya vessels or the posterior cerebral artery, consists of a perfusion reserve exceeding that of the other four regions in grade 2. In other words, relatively low rCBF reserves were observed in the anterior circulation areas.

The C/C ratios in all six regions did not change much in grade 3. C/C ratios indicate relative activity which decreases in regions with low rCBF reserves in comparison to normal or ischemic regions without vascular reactivity. We speculate that this is a result of the reactivity of cerebral vessels to decreases in acetazolamide throughout the entire brain in grade 3 is useful.

In conclusion, IMP SPECT imaging is useful for evaluating rCBF in patients with moyamoya disease. The acetazolamide test is useful for detecting cerebral blood flow reserve, including that in normal rCBF regions. The test can also prospectively detect disease progress.

REFERENCES
1969;20:288–299.