Redifferentiation of Iodine-Refractory BRAF V600E-Mutant Metastatic Papillary Thyroid Cancer with Dabrafenib

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Abstract

Purpose: To determine whether the selective BRAF inhibitor, dabrafenib, can stimulate radioiodine uptake in BRAF V600E-mutated unresectable or metastatic iodine-refractory papillary thyroid cancer (PTC).

Experimental Design: Ten patients with BRAF V600E-mutant iodine-refractory PTC were enrolled. Absence of radioiodine uptake on iodine-131 whole body scan obtained within 14 months of study entry was required. Each patient received dabrafenib (150 mg twice daily) for 25 days before thyrotropin α-stimulated iodine-131 whole body scan (4 mCi/148 MBq). Patients whose scan showed new sites of radioiodine uptake on whole body scan after treatment with dabrafenib, can stimulate radioiodine uptake in PTC, representing a potential new therapeutic approach for these patients. Clin Cancer Res; 21(5); 1028–35. ©2014 AACR.

Introduction

Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer. The incidence of PTC has dramatically increased over the past 40 years. In 2013, over 80% of the newly diagnosed thyroid cancers in the United States were PTCs (1). The majority of PTCs have activating mutations within gene that make up of the MAPK pathway. Approximately 50% of PTCs harbor BRAF-activating mutations (98%–99% encoding V600E), 20% have RET/PTC rearrangements, and a small percentage have NTRK rearrangements (2–5). Although PTC is usually indolent, tumors harboring BRAF mutations are more aggressive, with an increased risk of lymph node metastasis, extra-thyroidal extension, insensitivity to radioiodine and death (6).

Radioiodine is the most effective therapy available for patients with residual PTC after surgery, unresectable disease, or distant metastasis (7, 8). For patients whose tumors are either resistant to radioiodine de novo or become refractory to radioiodine over time, new therapies are needed. This is particularly true for patients with low volume, asymptomatic disease that is not rapidly progressive.

PTCs harboring BRAF mutations are insensitive to radioiodine in part due to low expression of the sodium-iodide symporter (NIS; refs. 9–12). When BRAF V600E is expressed in thyroid cancer cell lines, NIS expression and/or proper localization is suppressed, interfering with the cells’ ability to take up radioiodine (13–15). Insensitivity to radioiodine was overcome in a genetically engineered mouse model of BRAF V600E thyroid cancer by treatment with BRAF and MEK inhibitors, which induced reexpression of NIS and radioiodine uptake (16). In humans, the MEK inhibitor, selumetinib, increased radioiodine uptake in 12 of 20 patients with iodine-refractory differentiated thyroid cancer and led to significant tumor shrinkage in 5 of 8 patients treated with radioiodine (17). Together, these results demonstrate the potential clinical benefit of an iodine resensitization approach by pretreating patients with MAPK pathway inhibitors.

In BRAF-mutant thyroid cancers, direct inhibition of BRAF may be more effective than downstream MEK inhibition in stimulating NIS reexpression and radioiodine uptake (16). Therefore, we investigated the potential of the selective BRAF inhibitors.
Translational Relevance
Radioactive iodine is a highly specific and effective treatment for patients with differentiated thyroid cancer that is residual after surgery, unresectable, or metastatic. However, many patients have primary resistance to radioiodine or become refractory over time. Mutations in the MAPK pathway are frequent in thyroid cancer, and prior studies have shown that inhibiting this pathway can restore radioiodine uptake in thyroid cancer cells. This trial treated patients with iodine-refractory, BRAF-mutant papillary thyroid cancer with a short course of the BRAF inhibitor dabrafenib. This led to new radioiodine uptake in the majority of patients, leading to dramatic tumor responses. Our study adds to growing evidence for the potential clinical efficacy of this novel iodine resensitization approach in this difficult-to-treat patient population.

Patients and Methods

Patient selection
Eligible patients had histologically confirmed PTC that was metastatic or unresectable and harbored a mutation encoding BRAF V600E. Additional inclusion criteria included: absence of tumor iodine-131 uptake on whole body scan within 14 months of study entry (either low-dose, 74–148 MBq or high-dose, ≥1.1 GBq), evaluable disease by CT scan or ultrasound, age ≥18 years, Eastern Cooperative Oncology Group performance status ≤1, and adequate liver, renal, and bone marrow function. Exclusion criteria included prior treatment with BRAF or MEK inhibitors, brain metastases, symptomatic, large volume, or rapidly progressive disease (PD), as judged by the treating physician, and prolonged QTc interval. The study (ClinicalTrials.gov Identifier NCT01534897) was approved by the Institutional Review Board of the Dana-Farber/Harvard Cancer Center (Boston, MA). All patients provided written informed consent. Dabrafenib was provided by GlaxoSmithKline, thyrotropin α was purchased from Genzyme, and iodine-131 was purchased from Jubilant Drax Image Inc.

Treatment
Patients were treated with dabrafenib 150 mg orally twice daily until their diagnostic radioiodine scan was performed on day 25. Adverse events (AE) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Patients began a low-iodine diet on day 9. On days 21 and 22, each patient received thyrotropin α 0.9 mg IM, and on day 23, each received 148 MBq iodine-131. A whole body scan was performed on day 25. Spot urinary iodine measurements were performed before each scan to exclude intake of excess iodine. Dabrafenib was discontinued if there was no radioiodine uptake on whole body scanning. If radioiodine uptake was seen (in any abnormal site—new uptake at all known sites of disease was not specifically required), patients continued on dabrafenib and a low-iodine diet for 2 additional weeks. On day 37, iodine-131, 5.5 GBq, was administered (after thyrotropin α for 2 days). On day 42, a whole body scan was performed and dabrafenib was discontinued. Patients continued to receive their usual levothyroxine suppressive therapy throughout the protocol.

Whole body scanning
Whole body scans were performed using a dual head, large field of view γ camera (Siemens Symbia S, Siemens Medical Systems) equipped with high energy collimation 2 (for diagnostic 148 MBq dose) or 5 (for treatment 5.5 GBq dose) days after administration of iodine-131. Immediately before imaging, patients were injected with one mCi (37 MBq) of 99mTc pertechnetate to permit anatomic localization of lesions, a routine procedure at our institution. Simultaneous dual tracer iodine/pertechnetate images were obtained for anatomic localization. Anterior and posterior planar spot images of the head and neck were recorded for 15 minutes using a 256 × 256 image acquisition matrix. Images of the chest, abdomen, and pelvis/proximal thighs were recorded for 10 minutes each. For each focus of abnormal radioiodine uptake identified by the nuclear medicine physician, a region of interest size was correctly matched to the lesion and did not include extended artifactual uptake. Therefore, "star" artifacts did not obscure any areas of bona fide uptake. A radioiodine standard of approximately 100 microcuries (3.7 MBq) was prepared and imaged. All areas of abnormal radioiodine uptake were identified. The uptake within these regions was quantified as a percentage of the total administered radioiodine dose, based on counts recorded from the iodine-131 standard after correcting for radioactivity decay. The images in all patients were interpreted in a blinded fashion by an experienced nuclear medicine physician.

Baseline scans were performed both at Massachusetts General Hospital (MGH, Boston, MA; n = 4) and at outside (n = 6) facilities, either after rhTSH injection or after thyroid hormone withdrawal, with serum TSH >25 μIU/mL. All baseline scans were reviewed by the same nuclear medicine physician who interpreted the on-treatment scans, to confirm negative baseline status.

Tissue genotyping
Mutation detection in DNA-isolated, formalin-fixed, paraffin-embedded archival samples was performed at MGH with the SNaPshot multiplexed allele-specific tumor genotyping analysis as described previously (18). For one patient, BRAF mutational status was determined by real-time PCR assay performed by NorDx Laboratory.

Data analysis
The primary endpoint was the percentage of patients with dabrafenib-induced radioiodine uptake determined by whole body scan. Secondary endpoints included best tumor response at three months after radioiodine treatment according to RECIST.
1.1 and change in serum Tg concentration from baseline to 3 months after radioiodine treatment.

### Results

#### Study patients

Figure 1 shows the study schema. Ten patients were screened for the study, deemed eligible, and were enrolled between July 2012 and July 2013. Clinical characteristics of the 10 patients are presented in Table 1. The median age was 66 years (range, 61–84 years); 6 patients were male and 4 patients were female; 5 had classical variant, 4 had tall cell variant, and 1 had clear cell PTC. Although evidence of disease progression was not required for study entry, 5 patients had progression per RECIST v1.1 within the 14 months before enrollment. Four of the 5 patients who had PET imaging before study entry had 2-[18F]-fluoro-2-deoxy-D-glucose (FDG)-avid disease. All patients had been previously treated with radioiodine (median, 2 treatments; range, 1–4; all patients received at least one 5.5 GBq treatment dose). Three patients received prior external beam radiotherapy; no patient had received prior cytotoxic chemotherapy or targeted therapy. Baseline serum TSH range was 0.02 to 1.09 μIU/mL (median = 0.05).

### Efficacy

Six of 10 patients (60%) developed new radioiodine uptake while on dabrafenib, including all 4 patients with tall cell and 2 of 5 patients with classical variant PTC (Supplementary Table S1). Urinary iodine measurements confirmed that in patients with negative whole body scans, the absence of radioiodine uptake was not due to contamination by excess dietary iodine (Supplementary Table S2). Three of 4 patients with FDG-avid and one patient with FDG-negative disease developed new radioiodine uptake while on dabrafenib (Supplementary Table S1). New radioiodine uptake was found in 4 of 5 patients with documented PD and in 2 of 3 patients documented to have stable disease (SD) within 14 months before enrollment (Supplementary Table S1), and as expected, scans after the 5.5 GBq iodine-131 dose revealed novel sites not appreciated on the lower dose scans (Supplementary Fig. S2).

Figure 2A and B demonstrates a typical patient’s negative whole body scan before protocol entry. Fig. 2C demonstrates new radioiodine uptake in known sites of disease on dabrafenib. Supplementary Fig. S1 displays the pre- and posttreatment radioiodine scans in the 6 patients with new uptake. Physiologic uptake in sites such as the salivary glands, nasopharynx, and stomach was not affected by dabrafenib (Fig. 2 and Supplementary Fig. S1).

Six months after treatment with radioiodine, there was a reduction in the size of target lesions on CT imaging in 5 of the 6 treated patients (Fig. 3). Two patients met criteria for partial responses (PR; Figs. 3 and 4), including one with a nearly 60% reduction in the size of the target lesion, a mediastinal lymph node metastasis (Fig. 4A). Of the 4 patients who were treated with radioactive iodine with SD, 3 demonstrated a reduction in the size...
of the target lesions (by 12%–20%) and one had a slight increase (3%). By comparison, 1 of 4 patients who failed dabrafenib-induced radioiodine redifferentiation experienced PD, while the other three patients had SD (Supplementary Table S1). Although TSH-suppressed Tg concentrations decreased in 4 of 6 patients with new iodine-131 uptake at 3 months, the differences were not statistically significant (Table 2). It is worth noting that serum Tg concentration increased in 2 patients with new radioiodine uptake, both of whom had PRs, whereas serum Tg at 3 months increased in all 4 patients without radioiodine uptake (Table 2). These increases are not accounted for by variation in the degree of TSH suppression (Supplementary Table S3). Although rising Tg is generally indicative of tumor growth, the target lesions in both patients maintained their decreased size following radioiodine treatment, and no new foci of disease have been apparent on CT imaging.

Safety
All patients completed the full course of dabrafenib without dose modification. There were no unexpected AEs. AEs occurring in more than a single patient included new skin lesions or changes (80%), fatigue (50%), gastrointestinal symptoms (50%), electrolyte abnormalities (50%, two with hypocalcemia and one each with hypophosphatemia, hyperglycemia and hyponatremia), palmar-plantar erythrodysesthesia (PPE; 40%), headache (30%), nausea (20%), weight loss (20%), creatinine increase (20%), and epistaxis (20%; Table 3). One of the skin lesions was a new squamous cell carcinoma attributed to dabrafenib that was excised with clear margins. Other skin changes included darkening skin (20%), actinic keratosis (20%), and verrucous keratosis (20%). The hypocalcemia and PPE AEs were grade 2. All other AEs were grade 1. All AEs resolved upon completion of the study treatment. There were no AEs attributed to iodine-131.

Discussion
Post-surgical radioiodine therapy remains the standard of care for patients with potentially aggressive or advanced differentiated thyroid cancer. On the basis of randomized phase III trial results, the multikinase inhibitor, sorafenib, was recently approved by the FDA for patients with locally advanced or metastatic iodine-refractory thyroid cancer (including Hürthle cell, papillary, follicular, and poorly differentiated; ref. 19). Compared with placebo, sorafenib extended progression-free survival (PFS) from 5.8 months to 10.8 months. PRs were noted in 12.2% of patients. Of note, drug toxicities were frequent and required dose reductions or discontinuation of therapy in many patients. In addition, self-reported quality of life scores were lower in the sorafenib group than in the placebo group, despite the PFS benefit (20). Thus, although new therapies, such as sorafenib and other tyrosine kinase inhibitors (TKI), are emerging for patients with iodine-refractory disease, treatment with a TKI may not be appropriate for all patients after weighing the possible risks against the potential for benefit. This may be
particularly true for patients who are asymptomatic and have low-volume, slow-growing disease. For patients whose tumors are either resistant to radioiodine de novo or become refractory to radioiodine over time, more effective therapeutic approaches with less toxicity are needed. Redifferentiation of advanced thyroid cancer to facilitate treatment with radioiodine represents a novel approach for iodine-refractory patients for whom treatment with a TKI may not be appropriate. Preclinical studies in vitro and in genetically engineered mice have demonstrated that inhibitors of the MAPK signaling pathway can restore iodine uptake in \(BRAF\) V600E-mutant, iodine refractory thyroid cancer (11, 13, 14, 16). Blockade of this pathway with the MEK inhibitor, selumetinib, for redifferentiation and enhancement of radioiodine uptake in iodine-refractory thyroid cancer in humans was recently demonstrated (17). Notably, all 5 patients with \(RAS\)-mutant follicular thyroid cancer experienced selumetinib-induced increase in radioiodine uptake, while only 4 of the 9 patients with \(BRAF\) mutations developed uptake.

Our results with the selective BRAF inhibitor, dabrafenib, provide additional support for the hypothesis that MAPK pathway inhibition can restore sensitivity to radioiodine by facilitating redifferentiation of iodine-refractory advanced thyroid cancer. The percentage of patients with new or enhanced radioiodine uptake in \(BRAF\)-mutant PTC is similar with dabrafenib (6/10) and selumetinib (4/9); taken together, these data indicate the potential for MAPK pathway inhibitors to reverse insensitivity to iodine-131 in these more aggressive thyroid cancers. Although not prespecified, using a one-sample exact binomial test with a one-sided type 1 error of 10%, with our study design there would have been 85% power to rule out a null hypothesis of new uptake in 5% of patients (5% was adopted as the null hypothesis in the selumetinib study as well) and target a rate of 30% if at least 2 patients demonstrated new uptake.

There are several important differences between our trial and the selumetinib trial by Ho and colleagues (17). First, our study of dabrafenib was limited to \(BRAF\) V600E-mutant, whereas the selumetinib study was not limited to a specific genotype. Second, we used traditional iodine-131 whole body scanning with quantification of regions of interest to determine radioiodine uptake; Ho and colleagues used iodine-124 PET-CT lesionosimetry to predict which patients were most likely to respond to radioactive iodine. Iodine-124 PET-CT has two potential advantages over traditional iodine-131 whole body scanning: it can more accurately quantify iodine uptake in individual...
Dabrafenib Stimulates Radioiodine Uptake in Thyroid Cancer

Table 2. Change in thyroglobulin levels

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>New 131I uptake</th>
<th>RECIST response % at 3 mo</th>
<th>RECIST response % at 3 mo</th>
<th>RECIST response % at 3 mo</th>
<th>RECIST response % at 3 mo</th>
<th>Before dabrafenib (day 1)</th>
<th>Before 148 MBq iodine-131 scan (day 21)*</th>
<th>3 mo after radioiodine therapy</th>
<th>6 mo after radioiodine therapy</th>
<th>% change 3 mo</th>
<th>% change 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>+.7</td>
<td>SD</td>
<td>656</td>
<td>656</td>
<td>2,533</td>
<td>742</td>
<td>nd</td>
<td>13%</td>
<td>na</td>
<td>61%</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>+.4.4</td>
<td>SD</td>
<td>299</td>
<td>583</td>
<td>106</td>
<td>29.8</td>
<td>17.80</td>
<td>–68%</td>
<td>90%</td>
<td>61%</td>
</tr>
<tr>
<td>3</td>
<td>Y</td>
<td>+.6.1</td>
<td>SD</td>
<td>46.2</td>
<td>120</td>
<td>14.8</td>
<td>17.80</td>
<td>–68%</td>
<td>61%</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>4</td>
<td>Y</td>
<td>–56.6</td>
<td>PR</td>
<td>34.5</td>
<td>86.1</td>
<td>99.9</td>
<td>nd</td>
<td>190%</td>
<td>na</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>–3</td>
<td>SD</td>
<td>42.3</td>
<td>110</td>
<td>108</td>
<td>nd</td>
<td>155%</td>
<td>na</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>6</td>
<td>Y</td>
<td>–20.1</td>
<td>SD</td>
<td>115</td>
<td>36.7</td>
<td>111</td>
<td>nd</td>
<td>–3%</td>
<td>na</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>UN</td>
<td>SD</td>
<td>37.7</td>
<td>16.4</td>
<td>42</td>
<td>11%</td>
<td>11%</td>
<td>na</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>8</td>
<td>Y</td>
<td>–38.9</td>
<td>PR</td>
<td>46.2</td>
<td>7</td>
<td>99.7</td>
<td>138.00</td>
<td>116%</td>
<td>199%</td>
<td>na</td>
<td>61%</td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>20.6</td>
<td>PD</td>
<td>14.5</td>
<td>16.5</td>
<td>25.2</td>
<td>30.80</td>
<td>60%</td>
<td>112%</td>
<td>na</td>
<td>61%</td>
</tr>
<tr>
<td>10</td>
<td>Y</td>
<td>–17.6</td>
<td>SD</td>
<td>2.6</td>
<td>8.9</td>
<td>1</td>
<td>1</td>
<td>–62%</td>
<td>–62%</td>
<td>na</td>
<td>61%</td>
</tr>
</tbody>
</table>

aTSH was administered on days 21, 22, 35, and 36.

Also, the true threshold of iodine-131 uptake required for clinical benefit of radioiodine uptake between patients in the two studies.

In the current study, it is not possible to distinguish between tumor response resulting from a direct cytotoxic effect of dabrafenib and the induction of new radioactive iodine uptake. However, the short duration of dabrafenib therapy and the sustained response off dabrafenib suggest that a response to radioactive iodine is more likely. Furthermore, no responses were seen in patients who did not develop new radioactive iodine uptake. Notably, 6 of 10 patients demonstrated a clear increase in TSH after just 3 weeks of dabrafenib (Supplementary Table S3), before receiving radioactive iodine, and 4 of these 6 (patients 1, 2, 4, and 10) showed concomitant, clear increases in Tg during that same time frame (Table 2). For these patients, such increases may represent an increased thyroid hormone requirement induced by dabrafenib, leading to a rising TSH and TSH-stimulated Tg production, although a tumor differentiating effect of dabrafenib cannot be excluded. Other patients (e.g., patients 7 and 8) demonstrated decreased Tg (with relatively stable TSH) during the same time frame, suggesting an antitumor effect (or less likely inhibition of Tg release by dabrafenib). Finally, both patients with partial tumor responses by RECIST demonstrated both early (before low-dose radioactive iodine) and late (after high-dose radioactive iodine) increases in Tg over time (Table 2). Although the increases could suggest PD, the stability of these patients’ tumor responses and lack of new sites of disease on imaging could

<table>
<thead>
<tr>
<th>Table 3. Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>Skin*</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Electrolyteb</td>
</tr>
<tr>
<td>Gastrointestinalf</td>
</tr>
<tr>
<td>PPEa</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>Eye disorders*</td>
</tr>
<tr>
<td>Cr increase</td>
</tr>
</tbody>
</table>

NOTE: All toxicities were graded as mild (CTCAE v 4.0 grade 1) except for hypophosphatemia in patient 2 (severe but deemed unrelated to study drug), hypocalcemia in patient 7 (moderate), and PPE in patient 10 (moderate).

*Dabrafenib (2), actinic keratosis (2), verrucous keratosis (2), SCC (1), erythematous (1), papular (1), pinpoint (1), callus (1), pruritus (1), not specified (1).

*Darkening (2), hypocalcemia (1), hypophosphatemia (1), hypothyroidism (1), hypercalcemia (1).

*Nausea (2), weight loss (2), poor appetite (1), cramping (1), dysphagia (1), constipation (1).

aPPEs.

bHypophosphatemia (1), hypocalcemia (1), hypokalemia (1), hyperkalemia (1), hyponatremia (1), hypoglycemia (1).

cNausea (2), weight loss (2), poor appetite (1), cramping (1), dysphagia (1), constipation (1).

dPPE.

eWetary eyes (1), kaleidoscope vision (1–preexisting).
be due to a beneficial effect of dabrafenib on tumor differentiation. Additional study will be necessary to determine whether such early increases in TSH or Tg might provide an early indication of efficacy.

These data provide strong support for the concept that BRAF inhibition can induce radioactive radiiodine uptake in BRAF V600E-mutant iodine-refractory PTC, representing a form of tumor redifferentiation. Whether this approach will lead to long-term benefit for our patients is not yet known. Although 2 patients experienced PRs, as discussed above, their Tgs rose, and the declines in serum Tg overall in patients with new radioactive iodine uptake was modest. Compared with conventional or targeted chemotherapy, the ability to induce radiiodine uptake in iodine-refractory, advanced thyroid cancer has the potential advantage of requiring only a short course of minimally toxic targeted therapy to maximize the potential long-term therapeutic efficacy from radioiodine therapy.

Why only some patients with BRAF V600E-mutant disease developed new uptake with BRAF inhibition is not known. We do know that mutant BRAF-mediated inhibition of iodine transport is only partially ERK dependent, inhibition of the MAPK pathway with a BRAF or MEK inhibitor does not completely restore iodine uptake, and the effects of either RAF or MEK inhibitors on downstream signaling in thyroid cancer cells may be limited by feedback mechanisms (15, 16, 23). An important area of future investigation will be to study BRAF inhibitors in combination with other inhibitors of the MAPK or feedback pathways to achieve even more robust radioactive iodine uptake in BRAF V600E-mutant, iodine-refractory PTC (24, 25).

References

Disclosure of Potential Conflicts of Interest
G.H. Daniels is a consultant/advisory board member for Genzyme Sanofi. L.J. Wirth is a consultant/advisory board member for AstaZeneca and Eisai. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Rothenberg, E.L. Palmer, G.H. Daniels, L.J. Wirth
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.M. Rothenberg, D.G. McFadden, G.H. Daniels, L.J. Wirth
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.M. Rothenberg, E.L. Palmer, G.H. Daniels, L.J. Wirth
Study supervision: S.M. Rothenberg, G.H. Daniels, L.J. Wirth

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