Cutaneous adverse events in multiple sclerosis patients treated with daclizumab

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ABSTRACT

Objective: To analyze the spectrum and mechanisms of cutaneous adverse events (AEs) in patients with multiple sclerosis treated with daclizumab high-yield process (DAC-HYP).

Methods: A total of 31 participants in an institutional review board–approved open-label phase I study of DAC-HYP (NCT01143441) were prospectively evaluated over 42 months for development of cutaneous AEs. Participants provided written informed consent. Fifteen participants were naive to anti-CD25 therapy (cohort B), while 16 had received daclizumab (Zenapax; Hoffmann-La Roche) IV for 4–9 years (mean 5.8 years) prior to enrollment (cohort A). Immunohistochemistry was performed on pretreatment and posttreatment skin biopsies of normal-appearing skin (cohort B only) and on lesional biopsies in participants presenting with rash (both cohorts).

Results: Cutaneous AEs occurred in 77% of patients, the majority presenting with patches of eczema requiring no treatment. Moderate to severe rash developed in 6 participants (19%) and required discontinuation of DAC-HYP in 4 (13%). More severe rashes presented psoriasiform phenotype, but lesional biopsies lacked features of either psoriasis or drug hypersensitivity eruptions. Instead, irrespective of clinical severity, lesional biopsies showed nonspecific features of eczematous dermatitis, but with prominent CD56+ lymphocytic infiltrates. Pretreatment and posttreatment biopsies of normal-appearing skin demonstrated no histopathologic changes.

Conclusions: Observed cutaneous AEs are likely related to the immunomodulatory effects DAC-HYP exerts on innate lymphoid cells, including natural killer cells. Vigilance and timely management of skin reactions may prevent treatment discontinuation in participants with severe rash. *Neurology*® 2016;86:847–855

GLOSSARY

AE = adverse event; **BSA** = body surface area; **DAC-HYP** = daclizumab high-yield process; **H&E** = hematoxylin & eosin; **IL** = interleukin; **ILC** = innate lymphoid cell; **MS** = multiple sclerosis; **NK** = natural killer; **RRMS** = relapsing-remitting multiple sclerosis.

Daclizumab, a humanized monoclonal antibody against the α -subunit (CD25) of the high-affinity interleukin (IL)–2 receptor, is a promising new therapeutic for relapsing-remitting multiple sclerosis (RRMS). Surprisingly, daclizumab has little direct inhibitory effect on T cells; rather, by blocking IL-2 consumption by T cells, daclizumab enhances bioavailability of IL-2 for innate lymphoid cells (ILCs), which have high expression of intermediate-affinity IL-2 receptor.¹ This redirects differentiation of ILCs away from proinflammatory lymphoid tissue inducer cells/ILC3s toward regulatory CD56^{bright} natural killer (NK) cells, which can kill autologous activated T cells. Previous phase I/IIa trials of anti-CD25 therapy demonstrated >75% suppression of contrast-enhancing lesions² and benefit on clinical disability,³ subsequently confirmed in the phase II studies CHOICE⁴ and SELECT,⁵ and in the recently completed phase III study DECIDE.⁶ Daclizumab-driven expansion of CD56^{bright} NK cells correlates with clinical and imaging outcomes. While generally well-tolerated, in our experience cutaneous events are common, and rarely eruptions were severe enough to limit treatment continuation (reference 7

Supplemental data
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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

and current study). Here we report prospectively collected data, including lesional and nonlesional skin biopsies, on the cutaneous events in participants with multiple sclerosis (MS) treated with daclizumab high-yield process (DAC-HYP).

METHODS Participants. A total of 31 participants (13 female; mean age 40 years) with RRMS enrolled in a single-cohort, open-label phase I study of DAC-HYP 150 mg subcutaneously every 4 weeks were prospectively evaluated over 42 months for development of cutaneous events.

Fifteen participants were naive to anti-CD25 therapy (cohort B), while 16 received daclizumab (Zenapax; Hoffmann-La Roche, Branchburg, NJ) IV for 4–9 years (mean 5.8 years) prior to enrollment (cohort A). Cohort B eligibility criteria included RRMS or secondary progressive MS with active inflammation on MRI as determined by ≥ 3 contrast-enhancing lesions on a single screening scan.

Standard protocol approvals, registrations, and patient consents. The institutional review board approved the study and each patient provided written informed consent, with additional consent for photography. The study is registered on www.clinicaltrials.gov (NCT01143441).

Clinical evaluation. Patients underwent clinical evaluation monthly during the first year and every 6 months (with monthly verbal communications) for the remainder of the study. At each visit or communication, specific query was made regarding any cutaneous signs or symptoms. Determination of cutaneous events was based on patient report, verified by physical examination, and further characterized by dermatology consultation. Rashes were classified as mild (eczematous patches, localized eruption limited to $<5\%$ of body surface area [BSA]), moderate (diffuse eruption involving up to 50% of BSA), or severe (generalized eruption involving $>50\%$ of BSA).

Skin biopsies. Cohort B participants underwent 3-mm skin punch biopsy of normal-appearing medial arm skin at baseline

(before initiating treatment) and following 1 year of therapy. Additional biopsies were taken from affected areas in participants who developed moderate to severe rash and from 1 participant with mild rash. Patients did not receive topical or systemic corticosteroids prior to biopsies. Specimens were fixed in 10% neutral buffered formalin and routinely processed for H&E or immunohistochemistry stains.

Immunohistochemistry. Immunohistochemistry employed an automated immunostainer (Benchmark XT, Ventana Medical Systems, Tucson, AZ) or a Dako Autostainer Plus (Dako, Carpinteria, CA) in our Clinical Laboratory Improvement Amendments–approved clinical laboratory. Briefly, following deparaffinization and rehydration, slides underwent heat-induced antigen retrieval procedures specific for the antigen/epitope to be detected. Primary antibody incubations lasted 32 minutes to overnight depending upon the antibody used. Either the Ventana ultraView DAB detection kit for the Benchmark Ultra or the Envision+ horseradish peroxidase (mouse or rabbit) detection kit for the Dako autostainer were used for detection. Antibodies (clone) used, dilutions, and their sources were BCL-2 (124), 1:20, Dako; CD138 (MI15), 1:100, Dako; CD19 (LE-CD19), 1:50, Dako; CD25 (4C9), 1:100, Novocastra/Leica Biosystems (Buffalo Grove, IL); CD3 (F7.2.38), 1:400, Dako; CD30 (1G12), 1:50, Novocastra/Leica Biosystems; CD4 (1F6), 1:80, Novocastra/Leica Biosystems; CD56 (1B6), Novocastra/Leica Biosystems; CD8 (C8/144B), 1:50, Dako; FOX-p3 (Fox-p3), 1:100, Abcam (Cambridge, UK); Langerin (12D6), 1:200, Novocastra/Leica Biosystems; Leu-7/CD57 (HNK-1), 1:50, Becton-Dickinson (Franklin Lakes, NJ); Perforin (5B10), 1:10, Vector Laboratories (Burlingame, CA) (see table e-1 on the *Neurology*[®] Web site at Neurology.org).

RESULTS Incidence and clinical characterization. Twenty-three participants (77%) developed new or recurring cutaneous events (13 patients from cohort A, 10 from cohort B) during the observation period (figure 1, table e-2). No injection site reactions were observed.

In 20/23 participants (87%), eruptions were eczematous or psoriasiform in appearance, sometimes with features of both (figure 2). The majority of participants first presented with localized eczematous patches (figure 2, A–D). Most eruptions remained localized; however, in some the rash progressed. All moderate to severe rashes (6/23) had psoriasiform features, which persisted in later stages (figure 2, G and H). Patterns of psoriasiform involvement included palmar erythema with desquamation (figure 2, Q–S) and nail changes, most commonly nail pitting (I). In one participant, who later developed severe rash, nail changes evolved to paronychia with subungual, purulent exudate (J) and loss of nail plate (K). As the nail plate regrew (L), typical psoriatic pitting developed. Six patients developed mucosal lesions, most commonly recurring aphthous ulcers. Two unique, nonoverlapping patterns of facial rash, distinct from the more common facial eczematous patches, were observed, including eyelid edema with erythema (figure 2, M and N) and diffuse facial

Figure 1 Summary of mucocutaneous events

		# Subjects (%)	
General	All mucocutaneous events		23 (77)
	Mucosal events		6 (19)
Eczematous features	Eczematous patches		14 (45)
	Moderate		3 (10)
	Severe		3 (10)
Psoriasiform features			
Unique features	Face	Diffuse erythema	3 (10)
		Eyelids	5 (16)
	Palms		4 (13)
	Nails		3 (10)

Typical eczematous patches with well-circumscribed areas of erythema with overlying scale developed at month 9 (A), month 6 (B and C), and month 10 (D). Widespread eczematous patches developed at treatment months 12 (E), 9 (F), and 33 (G), in the latter patient becoming confluent 1 month later (H). Psoriasisiform nail changes developed at month 12 (I), evolving to destruction and loss of the nail plate by month 14 (J, K), followed by regrowth 6 months later (L). Facial rash with erythema and swelling of the eyelids (M, N; months 0.5 and 5, respectively) and diffuse facial erythema developed at month 30 (O). (P) Gingivitis at treatment month 10. (Q–S) Palmar erythema and desquamation at treatment month 33, month 12, and month 30, respectively.

erythema (figure 2, O). Scalp involvement resembling seborrheic dermatitis was observed in 6 patients. Eight patients presented cyclic exacerbations of skin symptoms, with eruptions typically flaring 2 weeks following DAC-HYP injection.

Skin manifestations developed in most patients within the first 12 months of treatment (range 1–34 months). There was no correlation between duration of treatment with anti-CD25 therapy (with either DAC-HYP or previous IV daclizumab) and

rash development; however, the earliest presentation of more significant rash (moderate or severe) was after 9 months of treatment with DAC-HYP, with mean time to onset of 20 months. Of the 3 severe rashes, 2 patients were from cohort A; of the 3 moderate rashes, 1 patient was from cohort A. Of note, of the 3 severe rashes, 2 initially presented as mild, only to worsen acutely at months 33 and 42, respectively. In 1 patient in cohort A, severe rash developed after 12 months of treatment; this patient had previously

received IV daclizumab for 8 years, during which he experienced transient eczematous eruptions that had resolved by the time of enrollment in this study.

Development of rash was not associated with MS disease course or with efficacy of anti-CD25 therapy in suppressing active CNS inflammation, regardless of severity of eruptions. Of the 3 participants who developed severe rash, the 2 from cohort A had clinically and radiologically stable MS for more than 7 years; the patient from cohort B had clinically and radiologically stable MS for almost 3 years.

A predisposing factor to eruptions was pretreatment history of eczema or seborrheic dermatitis, as DAC-HYP exacerbated flares of these preexisting conditions. Dry skin, especially in winter months, appeared to contribute to skin flares; photosensitivity, previously reported in DAC-related eruptions,⁷ was not a consistent feature, and some patients reported improvement of rash following sun exposure.

Mild and moderate rashes responded well to emollients and topical steroids, often requiring continuous or episodic treatment. Several patients with psoriasiform features received ultraviolet therapy, with good response.

Other mucocutaneous manifestations less clearly associated with DAC-HYP injections included contact dermatitis,⁴ urticarial rash following gadolinium exposure,³ and 1 patient each who presented with geographic tongue, perniosis, severe gingivitis, and granuloma annulare. With the exception of one, all patients with these manifestations also had the more typical rashes described above.

Four participants discontinued DAC-HYP due to skin manifestations; 3 of these had severe rash.

Histology and immunostaining. Nonlesional biopsies. Thirteen pretreatment and posttreatment biopsy pairs were obtained from cohort B participants to determine whether DAC-HYP causes discernable changes to nonlesional skin. Consistent with normal skin, rare CD4+ and CD8+ cells were seen in the dermis by immunohistochemistry at both time points. No histopathologic changes were observed between pretreatment baseline and 1 year post-DAC-HYP skin biopsies.

Lesional biopsies. Hematoxylin & eosin (H&E) of 9 lesional biopsies from 8 patients showed common, nonspecific features of eczematous dermatitis, irrespective of clinical categorization of rash, including the following (figure 3):

1. Foci of intercellular edema of spinous layer keratinocytes (spongiosis) (figure 3, red arrows).
2. Perivascular inflammatory infiltrates in the superficial dermis with rare, if any, eosinophils.
3. Focal lymphocytic infiltration of the epidermis (exocytosis) (figure 3, red arrows).
4. Mounds of hyperparakeratosis (thickened cornified layer with retention of epidermal keratinocytes nuclei) (figure 3, black arrows).

In participants with psoriasiform-appearing skin lesions, histologic hallmarks of psoriasis (such as neutrophilic exocytosis) were notably absent.

Immunostaining patterns are summarized in table e-1 and figures 4 and 5; as with H&E, common

Figure 3 Histology of skin eruptions during daclizumab high-yield process therapy

Hematoxylin & eosin sections of affected skin show inflammatory dermatitis, characterized by focal spongiosis with lymphocytic exocytosis (red arrows) and mounds of hyperparakeratosis (black arrows). (Original magnifications: A, C, D, F: $\times 400$; B, E: $\times 200$.)

features were found irrespective of clinical phenotype. Lymphocytic inflammatory infiltrates were present in the superficial dermis in all biopsies; CD3+/CD4+ T cells tended to localize in a perivascular distribution, whereas CD8+ cells were relatively predominant in areas of epidermal exocytosis (figure 4). Inflammatory infiltrates were BCL-2- and perforin-positive. CD19+ B cells were rare, without predilection for severity of rash or for particular clinical phenotype of the rash; when present, they were typically also associated with CD138+ plasma cells. Macrophages were present in severe rashes. Scattered CD25+ cells were present in most biopsies in variable numbers. FOXP3+ cells were abundantly present within the inflammatory infiltrates.

A consistent finding, most notable in moderate and severe rashes, was a robust population of CD56+ cells. CD56+ infiltrates were most prominent among rashes from cohort A compared to cohort B. However, the degree of CD56+ infiltration did not correlate with the degree of expansion of this cell population in peripheral blood (data not shown). This is consistent

with the observation that degree of expansion of CD56+ cells in the peripheral blood at steady state (available for 29/31 study participants) did not correlate with development of rash (mean absolute CD56^{bright} NK cell count 192,363.2 among participants who developed rash compared to 204,388.7 in those who did not; figure e-1).

DISCUSSION By implementing an active surveillance program to this open-label phase I trial primarily focused on determining the mechanism of action of DAC-HYP in MS, we observed a 77% incidence of cutaneous events, representing the most frequent adverse events (AEs) associated with DAC-HYP treatment. By comparison, the incidence of rash in placebo-controlled anti-CD25 therapy was 24% (vs 6% in placebo) in the phase II CHOICE study⁴ and 20% (vs 13% placebo) in the SELECT study⁵; in the phase III DECIDE study, cutaneous AEs were seen in 37% of DAC-HYP-treated patients vs 19% on active comparator treatment with interferon- β -1a,⁶ with rash (7% vs 3%) and eczema (4% vs 1%) being the most commonly reported skin manifestations.⁸ In the same study, serious cutaneous AEs were reported to be 2% vs <1%. We attribute the significantly higher incidence of cutaneous events in the current study to focused prospective collection with close examination for potentially subtle skin findings. Indeed, if only moderate and severe rashes are considered, the incidence of 19% is closer to that reported previously. While the prolonged treatment course in our cohort may have contributed to an increased incidence, we recognize the open-label design might also overestimate the occurrence of cutaneous events as a result of DAC-HYP treatment. Nevertheless, a clear cyclic pattern or temporal relationship to DAC-HYP dosing observed in 8/31 patients (25.8%, including all 3 participants with cutaneous severe AEs that required discontinuation of the drug) strongly suggests these events are drug-related.

There is scant information in the literature regarding cutaneous adverse reactions resulting from treatment with anti-CD25 for conditions other than MS. In the setting of various short-term treatment regimens used for prevention of solid organ transplantation rejection, dermatologic complications have not been reported. Similarly, a 6-week treatment course of IV daclizumab for the treatment of ulcerative colitis was not associated with cutaneous adverse reactions.⁹ In these studies, concurrent immunosuppressive therapies may have been a confounding factor. In contrast, in reports of a short course of daclizumab monotherapy (1 mg/kg every other week for a total of 5 doses) for treatment of pure red-cell aplasia, rash occurred in up to 45% of participants. In these

Figure 4 Immunohistochemistry of daclizumab high-yield process skin eruptions

Biopsy from a patient with severe rash. Immunohistochemical staining of lymphocytic infiltrate reveals superficial perivascular inflammation with exocytosis (Original magnification: $\times 400$.)

Figure 5 Biopsies from patients with rash

(A) Severe, (B, C) moderate, and (D) mild rash. Immunohistochemical staining of biopsies reveals lymphocytic superficial perivascular inflammation with exocytosis. (Original magnifications: $\times 200$.)

patients, previous thymectomy was reported to predispose participants to development of immune-mediated adverse reactions including rash.¹⁰ With more prolonged treatment regimens (6 months or greater) for management of immune-mediated disease including noninfectious uveitis, dermatologic adverse reactions are described with incidence from 13% to 58%.^{11–15} Biopsies of rashes demonstrated findings of eczematous dermatitis with acanthosis, parakeratosis,¹³ focal spongiosis, and dermal lymphocytic infiltration,¹⁶ similar to the histology in this cohort and consistent with previously reported histopathology in MS.¹⁷

Drug hypersensitivity reactions produce a wide variety of patterns, most frequently morbilliform exanthems (59.6%), classically grouped into 4 types based on the Gell and Coombs classification.¹⁸ However, medications capable of altering normal immune networks can induce adverse cutaneous reactions that are a direct or indirect consequence of the biological activity of the drug, rather than a hypersensitivity reaction. Examples include tumor necrosis factor- α inhibitors,¹⁹ captopril,²⁰ tyrosine kinase inhibitors,^{21,22} gold,²³ and rituximab.²⁴ This type of

pharmacologic immunomodulation is the most likely explanation for the eruptions seen in patients undergoing treatment with DAC-HYP.

Clinically, the eruptions were characterized by simultaneous/concomitant phenotypically distinct patterns: eczematous and psoriasiform eruptions. Initial, localized eruptions had predominantly eczematous features, but in the subset of participants who went on to develop more widespread moderate and severe eruptions, features more characteristic of psoriasis of the skin and nails developed. Despite phenotypic differentiation of eczematous (mild) vs psoriasiform (moderate to severe) features on clinical examination, the lesional pathology was surprisingly uniform, comprised of nonspecific features of eczematous dermatitis, but not classic psoriasis vulgaris. Notably, histologic changes of classic drug eruption, such as interface dermatitis with dermal eosinophilic infiltrate, were not seen in our study or in previous reports.^{7,17} Nonlesional pre- and post-DAC-HYP skin biopsies were performed to provide insight into potential daclizumab-induced changes in the skin. While immunohistochemistry analysis of 13 immune-related markers did not detect any histologic

changes in resident immune cell populations in normal skin following 1 year of treatment with DAC-HYP, we cannot rule out more subtle, molecular changes induced by anti-CD25 therapy that might affect skin reactivity. Immunohistochemistry of lesional biopsies was more informative and suggests that accumulation of CD56+ cells, which likely represent NK cells (although we cannot exclude cytotoxic CD8+/CD56+ T cells), is the hallmark of DAC-HYP-related skin inflammation. This conclusion is supported by observed activation and expansion of CD56^{bright} NK cells by daclizumab in the blood²⁵ and inflammatory sites, such as CSF²⁵ of patients with MS, and notable low numbers of infiltrating CD56+ cells in primary spongiotic dermatitis.²⁶ Interestingly, CD56+ infiltration in lesional biopsies did not correlate with the degree of peripheral expansion of NK cells, suggesting specific recruitment or retention of this cell population to the inflamed cutaneous compartment rather than proportional (nonspecific) infiltration by peripheral inflammatory cells.

NK cells belong developmentally to a larger population of ILCs. ILCs are strategically positioned at pathogen entry sites such as skin and mucous membranes, where they maintain functional integrity of the epithelial barrier and respond to stress signals released by epithelial cells by expressing immune functions that overlap and are synergistic with polarized effector T cells. ILCs are classified into 3 groups (ILC1, ILC2, and ILC3), each with a distinct cytokine production profile. NK cells (including CD56^{bright} immunoregulatory NK cells), able to produce interferon- γ , are included among ILC1. ILC2 cells predominantly produce IL-5 and IL-13, while ILC3 cells produce IL-17 and IL-22.²⁷ ILCs play a role in the development of some skin disorders, such as ILC2s in atopic dermatitis or ILC3s in psoriasis.²⁸ Interestingly, daclizumab skews differentiation of common ILC precursors away from ILC3s toward ILC1/CD56^{bright} NK cells.²⁹ We speculate whether daclizumab-driven changes in ILC differentiation, while beneficial for CNS disease, may lead to enhanced skin reactivity.

The notable lack of neutrophilic or eosinophilic infiltrates in lesional biopsies of DAC-HYP-treated patients, which would accompany ILC3- or ILC2-driven pathology, respectively, suggests DAC-HYP-induced rashes may be either driven directly by ILC1s/NK cells^{30,31} or by effects on adaptive immunity. The latter scenario could be mediated by daclizumab's inhibitory role on CD4+FoxP3+ Tregs.^{17,32} CD4+FoxP3+ Tregs home to skin and suppress weakly or moderately activated effector T cells, thus normally preventing exuberant inflammatory responses to minor insults or normal flora.³³ FoxP3+

staining is not exclusive to regulatory cells, but is seen transiently in all activated T cells. Thus single-marker histopathologic staining, as used in this study, cannot reliably differentiate true regulatory FoxP3+ T cells (which would also be CD4+) from activated (non-regulatory) effector T cells. While FoxP3+ staining was present in lesional biopsies from DAC-HYP patients, this did not appear to overlap with CD4+ staining. In fact, exocytosing T cells in the epidermis expressing FoxP3 were predominantly CD8+. Thus, in our view it is most likely that daclizumab-driven inhibition of FoxP3 Tregs contributes to heightened skin reactivity seen in these patients.

In view of the robust efficacy of DAC-HYP on the MS disease process, it is desirable to minimize the burden of any side effects that might reduce compliance. Open questions are whether it is possible to predict which patients will develop severe cutaneous complications, whether eruptions can be prevented, and how best to treat them when they do develop.

In our experience, all patients benefitted from regular use of emollients. Patients who developed psoriasisiform features and moderate to severe rash responded well to topical steroids or ultraviolet therapy. Two of the 3 patients with moderate rash were able to remain on DAC-HYP therapy with intermittent topical steroid application. For such patients requiring chronic management of cutaneous symptoms, future studies might address whether topical calcineurin inhibitors, commonly used for the treatment of chronic eczematous conditions, might be a viable long-term steroid-sparing strategy.

Reassuringly, across the spectrum of severity, no patients with daclizumab-related rash incurred scarring or permanent injury to nail matrix; similarly, the previously reported patient with alopecia universalis had no permanent hair follicle injury.⁷ While there do not appear to be long-term consequences of skin reactions, neurologists and patients should remain vigilant for these potential side effects and implement early, proactive management.

AUTHOR CONTRIBUTIONS

Dr. Cortese contributed to the analysis and interpretation of the data and drafted the manuscript. J. Ohayon contributed to the analysis and interpretation of the data and revised the manuscript for intellectual content. K. Fenton contributed to the analysis and interpretation of the data and revised the manuscript for intellectual content. Dr. Lee contributed to the analysis and interpretation of the data and revised the manuscript for intellectual content. Dr. Raffeld contributed to the analysis and interpretation of the data and revised the manuscript for intellectual content. Dr. Cowen contributed to the analysis and interpretation of the data and revised the manuscript for intellectual content. Dr. DiGiovanna contributed to the analysis and interpretation of the data and revised the manuscript for intellectual content. Dr. Bielekova is responsible for the design and conceptualization of the study; she further contributed to the analysis and interpretation of the data and revision of the manuscript for intellectual content.

STUDY FUNDING

This study was funded by the intramural research program of the National Institute of Neurological Disorders and Stroke (NINDS), NIH, and by a Collaborative Research Agreement (CRADA) between NINDS and Abbvie/Biogen-Idec.

DISCLOSURE

I. Cortese, J. Ohayon, K. Fenton, C. Lee, M. Raffeld, E. Cowen, and J. DiGiovanna report no disclosures relevant to the manuscript. B. Bielekova is co-inventor on NIH patents related to daclizumab therapy and as such has received patent royalty payments from NIH. Go to Neurology.org for full disclosures.

Received May 1, 2015. Accepted in final form November 4, 2015.

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