**Dermatitis Herpetiformis**

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Dermatitis herpetiformis (DH), described over 100 years ago, is a life-long blistering skin disease that can appear at any age. Dapsone controls the rash effectively and has been used for over 50 years in the treatment of DH. Major landmark in the research of DH was 30 years ago the discovery of granular IgA deposits in the upper papillary dermis, and further differentiation of an autoimmune disorder termed now as linear IgA disease from DH. The finding of mostly asymptomatic gluten-sensitive enteropathy, that is, celiac disease, and the observation that in all patients with DH the rash also responds to gluten free diet (GFD) treatment have had an important impact on our understanding of DH as a part of the spectrum of celiac disease. An immunogenetic link, HLA-DQ2, joins DH and celiac disease also tightly together.

A novel hypothesis of autoimmune pathogenesis of celiac disease consists of deamidation of wheat gliadin by tissue transglutaminase, binding to HLA-DQ2 and its recognition by gut T cells with subsequent production of epithelial damaging cytokines, matrix degrading enzymes, and also IgA autoantibodies against tissue transglutaminase. In DH, a clinically silent but immunologically active celiac, disease in the gut could produce IgA antibodies crossreacting with the connective tissue in the skin, a hypothesis presented already for 30 years ago. In contrast to the major progress made in the characterization of the target antigens in various autoimmune blistering disorders, such as pemphigus, pemphigoid, and linear IgA disease, one of the main goals in the research on DH is still to resolve the enigma of IgA deposition in the skin, what is the antigen, and does IgA have any role in blister formation.

### Prevalence and Clinical Presentation

The prevalence rate of DH has been reported to be 39 per 100,000 in Sweden and 66 per 100,000, that is, one-fourth of that of celiac disease, in Finland, showing that DH is a common dermatological disease in these countries. During the last 20 years annual incidence of DH has been about 3 per 100,000 in a county of Tampere in Finland. In addition to the northernmost Europe, DH seems, and also celiac disease, to be frequent in Scotland and Ireland. Reports from Hungary and Italy suggests that in these countries DH is common among children. In the United States there is a study suggesting a moderate prevalence in Utah and reporting 6.5% familial incidence of DH. A similar high frequency of familial DH has also been found in Finland. In contrast to Caucasoids, DH seems very rare among Blacks and Asians, and only a very few patients have been reported from Japan and Singapore. These differences in the geographical distribution of DH may be dependent both on the immunogenetic (HLA) and environmental factors, such as high or low consumption of wheat and related cereal products.

Men slightly predominate among patients with DH whereas the opposite is true for celiac disease. The common age at onset of DH is 30 to 40 years, but DH can appear also at older ages or even in childhood. In my personal series of over 1000 patients, the oldest patient has been 92 years old and the youngest 3 years old. At present, however, DH appears in childhood in less than 5% of all patients. The onset of DH may be abrupt or incident and the time to get the diagnosis from a dermatologist may vary from a few weeks to many years. When gastroenterologists have become aware of the occurrence of rash in association with the observed jejunal villous atrophy, they also can pick-up patients with DH from their practices.

The predilection sites of DH are elbows, knees, buttocks, and scalp. In addition, upper back, abdomen, groins, axillae, and face can be affected but oral lesions are rare. The rash is polymorphic with small blisters. These are, however, often eroded and crusted because of intense itch and scratching. The presentation and the activity of the rash varies much from a patient to patient, but complete remissions are unfrequent in a normal, gluten-containing diet.

### Diagnosis

The clinical picture is often highly susceptible for DH, but linear IgA disease is always a diagnostic problem (Table 1). Difficulties in the diagnosis may arise if the rash is not present in the typical predilection areas or when DH resemble full-blown bullous pemphigoid. The symptoms and signs of mild DH are also easily masked if the patient has a concomitant itchy skin disorder such as atopic dermatitis. Therefore, the diag-
nosis of DH should always be based on the demonstration of granular IgA deposits in the dermal papillae. The preferred biopsy site for direct immunofluorescence is normal-appearing skin adjacent to an active lesion because lesional skin often yields false-negative results. Normal individuals or patients with celiac disease do not have IgA deposits in their skin. The only difficulty in direct immunofluorescence examination in DH is to differentiate the granular IgA deposition occurring sometimes along the entire dermoepidermal junction from the linear but homogenous deposition pattern typical of linear IgA disease.

Typical histopathologic features of DH are found in an early non-blistering lesion, and these consist of accumulation of neutrophils and a few eosinophils with formation of papillary micro-apsesceses. This finding is, however, not diagnostic because it occurs also in the linear IgA disease.

More advanced lesions in DH show subepidermal bullae, and at this point, the microscopic appearance is typical with other subepidermal inflammatory bullous processes. Because of the high sensitivity and specificity of granular IgA deposits in the diagnosis, we do not currently take biopsies for routine histopathological examination from the patients suspected to have DH.

Most patients with DH, but not those with linear IgA disease, have subclinical celiac disease (Table 2). Gastroscopic biopsies show classical jejunal villous atrophy in 75% of the patients with DH, and the remainder have minor mucosal changes with increased numbers of intraepithelial gamma/delta T lymphocytes. Serologic markers of damaged jejunal mucosa in DH include IgA class anti-actin, endomysium and tissue transglutaminase antibodies. As expected, the presence of these antibodies differentiate the patients with DH from those with linear IgA disease.

**Table 3. Immunogenetics and Disease Associations in Dermatitis Herpetiformis**

<table>
<thead>
<tr>
<th>Disease Association</th>
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<tr>
<td>90% of the patients have HLA-DQ2 (frequency in controls 25%)</td>
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<td>100% have subclinical or latent celiac disease</td>
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<tr>
<td>Immunopathological diseases reported in association with dermatitis herpetiformis:</td>
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<tr>
<td>- endocrinological diseases; thyroid disorders, insulin-dependent diabetes mellitus, Addison’s disease</td>
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<tr>
<td>- connective tissue diseases; Sjögren’s syndrome, systemic lupus erythematosus</td>
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<tr>
<td>- skin diseases; vitiligo, alopecia areata</td>
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<tr>
<td>Lymphoma risk significantly increased but appearance generally a rare event</td>
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* Gluten-free diet for over 5 years protects from lymphoma

**Table 2. Small Intestine in Dermatitis Herpetiformis**

<table>
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<th>Clinical Findings</th>
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<tr>
<td>A very few patients have gastrointestinal symptoms or signs of malabsorption suggestive for celiac disease</td>
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<tr>
<td>75% have flat jejunal mucosa or partial villous atrophy</td>
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<tr>
<td>25% show slight morphological changes with increased numbers of intraepithelial lymphocytes including gamma/delta receptor bearing T cells</td>
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<tr>
<td>IgA class autoantibodies against tissue transglutaminase/endomysium and against wheat gliadin detectable in the serum of most patients with jejunal villous atrophy</td>
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Genomic typing of patients with DH, as of patients with celiac disease, has shown strong association with class II HLA alleles DQA1*0501 and DQB1*0201 in chromosome six. These genes encode HLA-DQ2 heterodimer and they were carried by 86% of the Norwegian patients with DH and 25% of the controls (Table 3). The remaining 12% of the patients presented with the alleles DQA1*0301 and DQB1*0302 encoding the HLA-DQ8 heterodimer. Previous studies from England and the United States have encountered HLA-DQ2 in 95% and 100% of the patients with DH. The association between DQ2 and celiac disease including DH is one of the strongest observed between the class II region genes and immunologically mediated disease. HLA-DQ2 is in linkage disequilibrium with HLA-DR3, -B8, and -A1, and this extended haplotype is known to be associated with several autoimmune and immunopathological disorders such as insulin-dependent diabetes mellitus and systemic lupus erythematosus, which have been also reported in association with DH (Table 3). At present, it is seems that the HLA DQ locus explains only a part of the genetic susceptibility and several non-HLA candidate regions have already been identified in celiac disease.

The common genetic background of DH and celiac disease is also disclosed by family studies. Celiac disease is well known to cluster in families, and the same is true for DH. As many as 4.5% to 6.5% of the patients with DH have first-degree relatives suffering from DH and even higher number relatives with celiac disease. As in celiac disease, disease segregation in the DH families seems to follow the risk HLA haplotypes, and the number of affected parents, siblings, and children fits well to a dominant mode of Mendelian inheritance. The existence of monozygotic twins, one with DH and the other with celiac disease, is the stron-
gest evidence for the shared genetic background of these two diseases, and indicates that the development of the rash in DH does not need extra genes in addition to those present in the patients with celiac disease. For a dermatologist, the practical consequence of the increased risk of the first-degree relatives of patients with DH to contract celiac disease is to inform the DH patient on this possibility and advise serological screening whenever a relative is suspected to have even minor symptoms or signs suggestive for celiac disease.

Pathogenesis of Dermatitis Herpetiformis

The Binding Site and Origin of IgA Deposits

Granular IgA deposits in dermal papillae are characteristic for DH. They are deposited throughout the skin, but greater amounts seem to be present together with complement (C3) near the active lesions. First immunoelectron microscopic studies localised IgA deposits in close association with microfibrillar bundles of elastic fibers in the papillary dermis and in the dermo-epidermal junction below the basal lamina. By using immunogold techniques, large amorphous collections of IgA were seen in the dermis, sometimes adjacent to basement membrane or the extended anchoring plaque, but co-localization with the elastic-microfibrillar bundles by using antibodies against fibrillin could not be confirmed in a further study. To date, the exact site of interaction between IgA and a specified structure in DH skin is, therefore, still unknown. The absence of circulating IgA autoantibodies against any dermal components in the sera of patients with DH seems, however, to be a fact. This finding is in sharp contrast to linear IgA disease in which such autoantibodies have been of great help when characterising the target molecules in the skin.

To determine the origin of the cutaneous IgA deposits several authors have tried to isolate functional IgA antibody from DH skin. These efforts have failed because IgA in DH skin resists extraction with agents commonly used for elution of immune complexes, or then the specificity of eluted IgA has remained unknown. It has been documented that IgA1 is the dominant subclass, with either minimal or no deposits of IgA2 being found. Whether the IgA in DH skin is dimeric and contains J chain has not, however, been confirmed. Taken together, these findings suggest that the IgA in DH skin may not arise from a gastrointestinal source as previously thought. On the other hand, it is known that when the patients with DH adhere to a strict GFD for several months to years IgA and C3 deposits decrease and may disappear, and IgA has shown to return with the start of gluten containing diet. This leads to a hypothesis that circulating immune complexes originating from the gut and composed of IgA antibodies attached to antigen, possibly gluten, could be deposited into DH skin because of possible cross-reaction with an antigenic determinant such as “reticulin.” Circulating IgA immune complexes can be detected in the sera of patients with DH, and increased levels have been found after wheat ingestion. Similar IgA immune complexes, however, occur also in the sera of patients with celiac disease who have neither skin disease nor cutaneous IgA deposits, suggesting that these complexes do not play primary role in the cutaneous IgA deposition in DH.

There is now increasing amount of evidence showing that autoimmunity, and especially IgA antibodies to tissue transglutaminase, formerly called as endomysium antibodies, seem to play an important role in the pathogenesis of the gut lesions in celiac disease and obviously also in DH. It is possible that excess IgA tissue transglutaminase antibodies could be deposited also into the skin due to a cross-reactivity with cutaneous transglutaminases. Tissue transglutaminase is also involved in the intermolecular cross-linking of type VII collagen, that occurs near the areas where IgA deposits in DH skin are found. Future research will reveal if there is a dermal autoantigen in DH skin related to tissue transglutaminase, but again the possibility that a unique antigenic determinant exists in the skin of patients with DH but not in patients with celiac disease skin is enigmatic.

Blister Formation

The formation of clinically visible blisters in DH starts with formation of neutrophil micro-abscesses at the summits of dermal papillae. These are quickly transformed by edema into micro-vesicles which then coalesce to form a unilocular subepidermal bulla. The split occurs in lamina lucida and the whole process of blister formation takes about 24 hours. A few studies have focused attention what happens before the neutrophils appear. Serial biopsies from potassium iodide induced DH lesions have shown early accumulation of lymphocytes in the dermis. The lymphocytes are activated and consist of mainly CD4+ T cells which express both IL-4 and IL-5 mRNA. An upregulation of adhesion molecules in endothelial cells could ensue resulting in the subsequent influx of neutrophils and eosinophils. Moreover, IL-8, a strong chemoattractant for neutrophils, is expressed in the basal layer of epidermis in DH skin, and GM-CSF, an activator of neutrophils and inducer of IgA receptors, is found in the dendritic cells in the dermo-epidermal junction. In addition to cytokines, activation of complement cascade by IgA molecules could be one mechanism for neutrophil influx into the papillary dermis. Thus the neutrophils are able to migrate into the upper dermis, may bind to IgA in the dermal papillae, and release enzymes causing tissue damage and destroying of IgA depos-
its.64,69 It is, however, difficult to understand why the rash in DH has the predilection areas in the knees, elbows, and buttocks, though IgA is deposited also in the sites never involved in lesion formation. The most likely explanation for this unique distribution of the rash involves the influence of the local factors, either physical, inflammatory, or immunological.

The suction blister fluid from DH lesions contains collagenase and elastase, which could be derived from neutrophils and involved in basement membrane degradation. The expression of matrix metalloproteinases, collagenase-1 (MMP-1), and stromelysin-1 (MMP-3) mRNA’s are upregulated in basal keratinocytes surrounding neutrophil abscesses.71 MMP-3, in particular, seem to contribute to the formation of DH blisters by degrading basement membrane components such as type IV and VII collagens as well as laminin-1. Furthermore, urokinase plasminogen activator is upregulated in keratinocytes already before micro-abscresses are formed.72 At the same time, macrophages in perivascular infiltrates or migrating towards epidermis start to express MMP-13 mRNA.73 Taken together, these findings in DH indicate that proteases secreted by keratinocytes, macrophages, and neutrophils produce matrix degradation in the dermo-epidermal junction which then leads to blister formation. Interestingly, the early expression of MMP-1 in DH is in contrast with the results obtained in bullous pemphigoid, pemphigus, and epidermolysis bullosa acquisita in which the upregulation of interstitial collagenase is a late event and seems to require epidermal regeneration to take place.74

Small Intestine

The occurrence of small intestinal mucosal abnormality in DH was first reported in 1966, and shortly thereafter it was recognized as gluten-sensitive and indistinguishable from ordinary celiac disease.5,78 To date, it can be concluded that all children and adults with DH have celiac disease though most of the patients have no gastrointestinal symptoms or signs of malabsorption.7,18,77 The enteropathy in DH varies from flat mucosa to partial villous atrophy in about 75% of the patients, and the remainder show minor morphological changes and increased counts of intraepithelial lymphocytes.7,18,27,57,76–78 At present, it is well established that the patients with overt gastrointestinal symptoms represent only the top of the celiac iceberg and that there is latent form of celiac disease showing only minor mucosal changes.8,79 A certain population of intraepithelial lymphocytes, CD4–, CD8-negative, gamma/delta T cell receptor–bearing lymphocytes are closely associated with celiac disease and DH.33,80 The activation of these gamma/delta T cells, exclusively found within epithe-

<table>
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<th>Table 4. Treatment of Dermatitis Herpetiformis</th>
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<td>Gluten-free diet is a treatment of choice because the rash and enteropathy heals</td>
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<td>A combination with dapsone 50–100 mg daily at the beginning of the treatment is recommended due to the slow response to a gluten-free diet</td>
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<tr>
<td>After being on a strict gluten-free diet for several months to years about 80% of the patients can reduce markedly the dose or completely stop using dapsone, a drug which has potential for dose-related hematological side-effects</td>
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<tr>
<td>Oats can be included in the gluten-free diet but wheat, rye and barley are still strictly forbidden</td>
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Gluten-free diets seem to be effective in the majority of patients and are therefore the preferred treatment. However, in some patients, gluten-free diets alone are insufficient, and additional treatment may be required. There are two ways of treating patients with DH (Table 4): dapsone, or related drugs, and a GFD.6,7,84,85 Because it takes several weeks to months for the rash to respond to the diet, initial treatment suitable for most patients is to start with combination of dapsone and GFD. Both treatments have their advantages and disadvantages. Dapsone causes rapid relief in itching, and the rash subsides within 2 to 3 days. On the other hand, dapsone
has a risk for hematological and other side effects, and in contrast to GFD, it has no effect on the enteropathy. The total control of the rash with a GFD takes many months or years, but it does allow the patient to withdraw from dapsone completely. A GFD must be strict to be effective and can be socially disabling for the patient. GFD may, however, bring an improvement in the subjective well being that a patient may feel within 6 to 8 weeks of commencement of the diet treatment. The final advantage of GFD treatment in DH is that it reduces the risk for lymphoma.

Dapsone
Most patients with DH require 50 to 100 mg dapsone daily to control their symptoms but a few need higher dosage. The majority of patients tolerate dapsone well, but there is always a risk for dose-related hematological side-effects, which should be carefully considered especially in the elderly patient population. Dapsone 100 mg daily and higher dosages cause hemolysis leading to a fall in hemoglobin. This can cause problem in patients with ischemic heart or other vascular diseases. Patients with glucose-6-phosphate dehydrogenase and other genetic red cell abnormalities are prone to severe hemolysis and in them dapsone is contraindicated. Most patients on 100 mg of dapsone have a small degree of methemoglobinemia. This can manifest soon after taking the drug as headache, and may also cause management problems in patients who have associated ischemic diseases. Concomitant use of 800 units of vitamin E daily protects partially from dapsone-induced hemolysis and cimetidine 1.6 g daily reduces methemoglobinemia and headache caused by daily dose of 50 to 100 mg dapsone. Sensory or motor neuropathies may appear after long-term treatment with higher daily doses of dapsone and a simultaneous B12-vitamin deficiency may be an additional risk factor for this side effect. The most severe, though very rare, side effect from dapsone is agranulocytosis, which usually appears within the first few months of treatment.

Gluten Free Diet
GFD is the treatment of choice for the patients with DH because both the rash and enteropathy improve with the diet treatment. The rash responds to GFD regardless of whether the patient has flat or normal appearing jejunal mucosa. The diet has to be strictly gluten free to be successful, and some effect on dapsone dosage may be seen within 3 months of starting the diet. The mean time for cessation of dapsone therapy was in one study 25 months. About 90% of the Finnish patients adhere to a GFD, and after a mean follow-up of 10 years 47% of the patients had been able to stop using dapsone, 38% had reduced the daily dose by 50% or more, and only 15% of the patient had been unable to reduce the daily dose of dapsone during the diet treatment. In the absence of gastrointestinal symptoms and signs of malabsorption, the patients motivation for the strict diet seems to improve after a gastroscopy and resulting knowledge of the presence of small intestinal mucosal damage. Similarly, the decreased levels of serum IgA antigliadin or endomysium/transglutaminase antibodies observed during the first months of GFD treatment are good markers both for the patient and the dermatologist on the healing of the intestinal mucosa.

An early visit to a dietitian is important for successful GFD treatment, and a membership in the National Celiac Society brings circulars with up-to-date information on proprietary foods that are free of gluten. Wheat, barley, rye, and oats are excluded from the conventional GFD. Recently, it has been shown that the patients with celiac disease tolerate oats without any harmful effects on the small intestine, and interestingly, the rash in patients with DH is not activated by eating oats. The inclusion of oats in a GFD increases the variety of cereals that can be consumed, which may improve the compliance and also reduce the otherwise high cost of GFD treatment. The rash of some patients with DH is very sensitive to gluten, and intake of trivial amounts, such as one bottle of beer, may cause a flare-up of the rash. Wheat starch-based commercial gluten-free products are allowed to be labelled as gluten-free in Europe though they contain minute amounts of gluten. It has been questioned if these products are safe enough for the treatment, but no harmful effects could be detected on the small intestinal mucosa of either in patients with celiac disease or DH who were consuming these products. A possibility remains, however, that the minute amounts of gluten derived from the wheat starch products could be a reason for continuously active rash in a few patients with DH not responding to an ordinary GFD.

Prognosis
The patients with DH, as patients with celiac disease, have increased risk for lymphoma. Studies in large patient series from England, Sweden, and Finland have documented 100-fold, 5.4-fold, and 10-fold risks for developing lymphoma. A collaborative study from England and Finland showed a protective effect of GFD against development of lymphoma in patients with DH because all 8 lymphomas occurred in patients on a normal gluten-containing diet or in those who had been treated with a GFD less than 5 years. The majority of lymphomas reported in DH have been non-Hodgkin’s lymphoma, but lymphomas of B-cell origin and Hodgkin’s Disease have also been described. The risk of developing lymphoma in DH and celiac disease particularly in the gastrointestinal tract or associated lymphnodes (i.e., enteropathy associated T-cell lym-
phoma) may depend on long-lasting stimulation of lymphocytes, by gluten, giving rise to malignant transformation.

Although the patients with DH have increased incidence of lymphoma and autoimmune diseases, general mortality was not increased either in an English or Finnish patient series. Interestingly, the long-term survival rates were slightly but significantly increased among the Finnish patients with DH which could be the result of the fact that 93% of the patients adhered to a GFD. Similarly, a significantly lower than expected mortality rates from ischemic heart disease and lower levels of cholesterol, triglycerides, and apolipoprotein B was reported in DH patient series from England.

Conclusions

During the last 30 years the research on DH has brought up several important findings for dermatologists and scientists. The change from a blistering dermatological disease to a disorder in which both the skin and gut are sensitive to cereal proteins, and also treatable by a GFD, has been dramatic. The linkage to celiac disease revealed that DH is also a genetic disorder having a strong association with HLA-DQ2 and a tendency to cluster in families with celiac disease. Though granular IgA deposits in dermal papillae are pathognomonic for DH, and not present in the skin of patients with celiac disease, their antigenic specificity remains to be elucidated in contrast to autoantibodies in the linear IgA disease. The only circulating IgA autoantibody detected to date in DH is the antibody against tissue transglutaminase. This antibody is, however, specific for gluten-sensitive enteropathy (i.e., for celiac disease), and it may be involved together with DQ2-restricted, gliadin-specific T cell response in the pathogenesis of the gut lesion. This novel hypothesis on the autoimmune pathogenesis of gluten-sensitive enteropathy raises the question if there is also a dermal autoantigen in DH related to tissue transglutaminase.

The role of IgA, if any, in the blister formation in DH remains still to be elucidated. The observation that matrix metalloproteinases seem to be involved both in blister formation and small intestinal damage in DH is a new one and is a topic for further studies. Dapsone controls rapidly the blistering, but the combination treatment with a GFD is highly recommended. The damaged small intestine heals, the risk of lymphoma decreases, and after several months to years on the strict diet 80% of the patients with DH can markedly reduce the dosage or completely stop using dapsone, a drug which has a potential for many side effects. Patients with DH, like patients with celiac disease, are prone to develop associated autoimmune diseases, such as thyroid disease and Sjögren’s Syndrome, and future studies will disclose whether a long-lasting GFD treatment may be protective also against these disorders.

Acknowledgements

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Trade dollars were created for American merchants to use as currency in the world market. Many foreign coins had more silver than the standard United States silver dollar in circulation (412.5 grains of silver). Congress passed a new coin, called the Trade Dollar which had 420 grains of silver. It’s composition was 90% silver and 10% copper, the reverse of the coin states the purity of the coin as .900 fine silver. When these coins were in Chinese merchant coffers, they often took a small piece of the coin to verify the purity of the metal. These marks are called “chop marks” as depicted on the obverse of this coin.¹

REFERENCES: