SEBORRHEIC KERATOSES

I. "PSEUDO-EPITHELIOMATOUS HYPERPLASMA" (WEIDMAN)*

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At the American Academy of Dermatology and Syphilology annual meeting in Chicago on December 9, 1953, Dr. F. D. Weidman (1) presented slides of two lesions to the histopathologic conference, number W-15699 and number W-15806. Both lesions occurred in white males, ages fifty-five and fifty-eight. One was a solitary glistening lesion with a rough surface and suspicions of an angiomatous factor. This was of three or four months' duration and the microscopic diagnosis was seborrheic keratosis (with "pseudo-epitheliomatous hyperplasia"). The other lesion was of two years' duration and occurred near the right eye. The clinical diagnosis was questionable basal cell epithelioma and the pathologic diagnosis, seborrheic keratosis (pseudo-acanthoma).

In both cases the histopathologic picture was that of a prickle cell hyperplasia, or acanthoma, with pearl and whorl formation and a decided similarity to a prickle cell carcinoma or a kerato-acanthoma and with little or no suggestion of the usual picture of seborrheic keratosis.

Clinically, one lesion was a keratotic angiomatous papule or nodule and the other resembled a basal cell epithelioma. Thus, neither the clinical nor the microscopic picture of these lesions was suggestive of seborrheic keratoses. Indeed, several panel members did not accept Dr. Weidman's diagnosis but suggested others as follows: Inverted follicular keratosis (Helwig), squamous cell carcinoma, grade I (Lever), benign acanthoma of skin (Caro), squamous cell carcinoma, and basal cell carcinoma from sebaceous glands, (first and second cases respectively, W. Nickel). Others, (N. P. Anderson and H. Beerman) noted having seen such changes before with squamous cell features and pearls and whorls in seborrheic keratoses but not to such a degree (1).

Another section with a similar microscopic picture was presented as case number forty-three at the Histopathologic Session of the Pacific Dermatologic Association in Oakland, September 3, 1950, by Dr. N. P. Anderson (2). Clinically, this was a 2 cm. sized lesion anterior to the right ear, moderately elevated, deeply pigmented with crusting in the central portion. It was of ten years' duration, and suggested a malignant melanoma. Dr. Anderson's histopathologic diagnosis was seborrheic keratosis with basal cell carcinoma, and/or basal squamous carcinoma.

Most of the section consisted of acanthomatous epithelium with pearls and whorls as described before. However, at one side, some epithelium remained, which displayed basal cell pigmentation, and a network hyperplasia of epidermal cells enclosing islands of connective tissue; and which was recognizable as seborrheic keratosis.

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From our own clinic during a three-year period, eight lesions came to biopsy with this histologic picture of a prickle cell acanthoma showing pearls and whorls. In none of these was there much if any similarity to the usual microscopic picture of seborrheic keratosis. These eight sections can be described in summary as follows:

Hyperkeratosis was present and more marked than parakeratosis. The granular cell layer was normal, but absent under areas of parakeratosis. The epidermal hyperplasia was one of cells with the size, shape and staining properties of prickle cells. Pearl formation was marked, though sometimes the pearls were not as well demarcated as in carcinoma. Keratin cysts were present but much less numerous than pearls. Sometimes, though not always, the cells composing the pearls and cysts contained granules like the granular cell layer. Melanin pigment was usually sparse or absent in hematoxylin and eosin stained sections but occasionally was plentiful. Epidermal edema varied from marked to absent. Frequently, the papillary cutis contained dilated capillaries filled with red blood cells. Some extravasated red blood cells were occasionally found here also. An inflammatory infiltrate in the upper cutis was usually present but only moderate or sparse in amount. It was noteworthy that the epidermal cells were uniform, regular, and normal in size, shape and staining and that their nuclei too were

**Fig. 1.** This lesion was of three months' duration, and occurred anterior to the right ear of a forty-eight year old white female. It was a pigmented keratotic maculo-papule, and the clinical diagnosis was seborrheic keratosis. The unusual histologic picture, combining pearls and considerable accumulation of pigment, suggested a variant of malignant melanoma.
normal and uniform. Also, the basal cell layer was composed of only one layer of normal basal cells, which stained normally and did not show duplication or increased basophilia. (Figures 1, 2, 3 and 4.)

The not too rare occurrence of these lesions in our clinical material prompted an investigation of them, particularly in respect to their usual gross appearance, their relationship to seborrheic keratoses and their malignant potential.

REVIEW OF LITERATURE

The literature contains some references as to the occurrence of squamous cell features with anaplasia (prickle cell pearls and whorls) in seborrheic keratoses, and descriptions and photomicrographs of such lesions are also to be found.

Van Der Meiren and Achten (3) classified senile keratoses into three groups on the basis of a study of one hundred and twelve biopsies. They described all three groups as brownish lesions with a verrucous covering, so that their senile keratoses had the usual or accepted gross appearance of some seborrheic keratoses. Their figure 7, a photomicrograph illustrating group B ("aggravated atypicalness" of epithelium), seemed to be an instance of our acanthoma.

In 1926 and again in 1929, Freudenthal (4) (5) emphasized the distinction between benign seborrheic keratoses, and essentially premalignant senile keratoses. In the latter paper, he presented the case of a seventy year old man who had a tumor on the back, of ten to fifteen years duration. This lesion had an apparently clearing or less active centre and sharp borders. The upper portion

Fig. 2. A higher power view of the central portion of Figure 1
was red-brown and the lower portion brownish. He took two biopsies from this lesion. The biopsy from the upper portion he reported as a seborrheic verruca, and the lower one, as an atypical Bowen's disease. No illustrations were published in this article. Nevertheless, it is not unlikely that the instance of atypical Bowen's disease was really our acanthoma arising in or with a seborrheic keratosis.

In 1927, Kreibich (6) described an entity under the name of granuloma senile. The patient was a fifty-five year old woman, who had had some fifty typical seborrheic keratoses on the back for many years. During the three months prior to surgery, two of them ulcerated, and appeared as red nodular elevations, hazelnut and pigeon's egg size respectively. These red nodular elevations had brown, crusted, irregular, papillomatous surfaces, and were continuous with clinically typical seborrheic keratoses. Kreibich described the section of the lesion as showing ulceration and edema, but being similar to that of the adjacent seborrheic keratosis. Though the pre-operative diagnosis was carcinoma in a seborrheic keratosis, Kreibich considered the lesion benign. His published photomicrograph did not show much cell detail, but it would seem legitimate to classify this entity as seborrheic keratosis with acanthomatous change.

The lesion described by Johnson and Harvey (7) in 1930, under this same title of granuloma senilis, as an instance of the same disorder, does not seem to be related to Kreibich's case either clinically or histopathologically.

In 1940, Traub and Keil (8) discussed intra-epidermal nevi and presented a
photomicrograph (their Figure 1) of a lesion called intra-epidermal nevus with early squamous cell carcinoma by Satenstein. This also might be an instance of a seborrheic keratosis with acanthomatous features.

Sutton and Sutton (9) in their text book, "Diseases of the Skin", presented the opinion that seborrheic keratoses on irritation could change to a "medullary squamous carcinoma". Their photomicrographs (Figure 592, page 695) probably represent our acanthoma. They called this an intra-epidermal squamous carcinoma with intra-epithelial formation of pearls. Clinically this consisted of a chronic lesion on the neck, a slightly elevated seborrheal brownish plaque. They also described an entity called "squamous cell keratoses" which they believed to be comparatively benign squamous cell carcinomas of superficial location, arising in seborrheic keratoses.

Sachs, Mackee and Sachs (10) also reported on seborrheic verrucae in 1949 and divided these into seborrheic keratoses, having a smooth or slightly verrucous surface; and seborrheic verrucae, into which seborrheic keratosis gradually transformed as they grew older. The verrucae were larger, raised and with a definitely verrucous surface. They believed that seborrheic keratoses and seborrheic verrucae as defined above, had different malignant potentials. It was their opinion that basal cell carcinomas could arise from seborrheic keratoses; and that anaplastic epithelium could be seen in seborrheic keratoses but that prickle cell carcinomas did not develop here.
From seborrheic verrucae however, they believed basal cell and mixed cell carcinomas could arise, but prickle cell carcinomas also, though less frequently. These malignant transformations were not illustrated; and one can speculate again on acanthomatous changes in seborrheic verrucae.

In 1951, Caro and Szymanski (11) discussed seborrheic verrucae and described "nests of cells that are flat, seemingly polygonal, and pale staining and suggesting a malignant metaplasia within the keratosis". However, they believed these cells were really the same as the surrounding basal-like cells, but that their plane of presentation (sectioning) was confusing.

In 1951, Becker (12) discussed and classified seborrheic keratoses on the basis of a detailed study of two hundred and sixty-three specimens from two hundred and fifty-two patients. He found anaplasia in forty percent of his series of sections, always associated with parakeratosis and inflammatory infiltrate in the cutis, and he believed this change to be pseudo-carcinomatous rather than truly carcinomatous. He defined anaplasia as an alteration of cell polarity with irregularity in the size and shape of the nuclei.

Two of his photomicrographs (Figures 6 and 7) of an anaplastic seborrheic keratosis showed areas resembling our acanthoma and he quoted H. Montgomery's diagnosis of these sections—"An early verruca senilis, which is showing an early intra-epidermal epithelioma of Borst-Jadassohn squamous cell, grade I." The clinical description of this lesion is listed in the table that follows.

Weidman, in his comment on this paper, defined anaplasia as a transformation from basal cell type to squamous. He believed this to be a pseudo-epitheliomatous hyperplasia, associated with irritation and inflammation. (12)

A. C. Allen, (13) discussed variants of seborrheic keratoses. Some of his photomicrographs of these showed nests of prickle-like cells in seborrheic keratosis, and one section was typical of our acanthoma, (Page 711, plate 307E). The clinical description of this lesion was not given. He stated that basal cell, and prickle cell carcinomas, as well as variants could arise from seborrheic keratoses. He believed, too, that melanomas could arise from seborrheic keratoses. This is not a generally accepted belief. His photomicrograph of a melanoma arising from a pigmented seborrheic keratosis (Plate 413B, page 877) could be interpreted much more readily as a melanoma arising from a junction nevus. Finally, he classified the fibro-epithelioma of Pinkus as a seborrheic verruca—a viewpoint difficult to justify either clinically or histologically.

Thus the presence of marked whorling and swirling of prickle cells in recognizable seborrheic keratoses has been noted by several authors, and has been assumed to be due to inflammation and irritation by Becker and Weidman. Furthermore, the cases reported as carcinoma arising in a seborrheic keratosis would seem to be instances of the lesion under discussion.

Table I shows the clinical aspects of the preceding cases found described in the literature.

Traub and Keil's, and Becker's cases, microscopically were still recognizable as seborrheic keratoses. (Traub and Keil list their case as a hard nevus with
carcinomatous change, but from the photomicrograph published, it could well be a type of seborrheic keratosis and the clinical description does not rule this out.)

Microscopically, both Anderson and Freudenthal's cases showed typical seborrheic keratoses in portions of the lesion adjacent to the acanthoma, though in Anderson's case and presumably in Freudenthal's also, in the acanthoma itself, there was no suggestion of seborrheic keratosis-like appearance. Thus these four cases relate this prickle cell acanthoma to seborrheic keratoses, microscopically.

**CLINICAL OBSERVATION**

The clinical aspects of the eight cases from our own clinic are listed in Table II. The first case listed in Table II, from the clinical description, could not have
been a seborrheic keratosis, but must have been the entity described by Winer (14) as "the dilated pore." In this article, Winer does not mention the occurrence of acanthomatous change in his series of cases.

Thus, the seventeen cases listed in Tables I and II probably had the following clinical appearance or diagnoses:

<table>
<thead>
<tr>
<th>Race</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Description</th>
<th>Duration</th>
<th>Clinical Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>50 yr</td>
<td>F</td>
<td>Right nasolabial fold</td>
<td>Keratotic plug about 6 mm. by 3 mm. embedded in skin</td>
<td>8 years</td>
<td>Comedo concretion</td>
</tr>
<tr>
<td>White</td>
<td>48 yr</td>
<td>F</td>
<td>Anterior aspect, left leg</td>
<td>Horny lesion</td>
<td>5 to 6 months</td>
<td>Cutaneous horn</td>
</tr>
<tr>
<td>White</td>
<td>58 yr</td>
<td>F</td>
<td>Anterior surface of left anterior axillary fold</td>
<td>Erythematous tumor with keratotic top, pea size and shape</td>
<td>6 months</td>
<td>Vascular fibroma</td>
</tr>
<tr>
<td>White</td>
<td>41 yr</td>
<td>F</td>
<td>Right buttock</td>
<td>Not available</td>
<td>1 year</td>
<td>Pyogenic granuloma</td>
</tr>
<tr>
<td>White</td>
<td>41 yr</td>
<td>M</td>
<td>Abdomen at belt line</td>
<td>Verrucous fleshy lesion</td>
<td>Most of his life</td>
<td>Cellular nevus</td>
</tr>
<tr>
<td>White</td>
<td>54 yr</td>
<td>F</td>
<td>Left thigh</td>
<td>Not available</td>
<td>Not available</td>
<td>Nevus</td>
</tr>
<tr>
<td>White</td>
<td>60 yr</td>
<td>M</td>
<td>Left buttock</td>
<td>Not available</td>
<td>Not available</td>
<td>Cutis nevus</td>
</tr>
<tr>
<td>White</td>
<td>48 yr</td>
<td>F</td>
<td>Anterior to right ear</td>
<td>Pigmented keratotic maculopapule</td>
<td>3 months</td>
<td>Seborrheic keratosis</td>
</tr>
</tbody>
</table>

As mentioned previously, four of these cases showed histopathologic evidence of relationship to seborrheic keratoses. Furthermore, even the varied clinical appearances and diagnoses as above, did not rule out seborrheic keratoses.
In Becker's paper, of two hundred and thirty-four lesions with the microscopic diagnoses of seborrheic keratoses, the clinical diagnoses were:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Approx. Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrheic keratoses</td>
<td>152</td>
<td>65.0%</td>
</tr>
<tr>
<td>Nevus pigmentosus</td>
<td>29</td>
<td>12.0%</td>
</tr>
<tr>
<td>Verruca vulgaris</td>
<td>18</td>
<td>8.0%</td>
</tr>
<tr>
<td>Senile keratoses</td>
<td>10</td>
<td>4.0%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>10</td>
<td>4.0%</td>
</tr>
<tr>
<td>Granuloma pyogenicum</td>
<td>3</td>
<td>1.0%</td>
</tr>
<tr>
<td>Lentigo maligna and melanoma</td>
<td>3</td>
<td>1.0%</td>
</tr>
<tr>
<td>Adenoma sebaceum</td>
<td>2</td>
<td>1.0%</td>
</tr>
<tr>
<td>Psoriasis, foreign body tumor, tumor and papule, each</td>
<td>1</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

In addition, two hundred and forty-four sections from our clinic, representing about three years' accumulation, were reviewed, in all of which the microscopic diagnosis was seborrheic keratosis. The clinical diagnoses were:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Approx. Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrheic keratosis</td>
<td>176</td>
<td>72</td>
</tr>
<tr>
<td>Nevus</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma vs. nevus</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Verruca vulgaris</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Senile keratosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Prickle cell carcinoma</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Skin tags</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Thus, lesions with clinical appearances as described by these misdiagnoses, not infrequently have microscopic pictures of typical or recognizable seborrheic keratoses.

Apparently also, lesions with these same clinical appearances or with clinical appearances of seborrheic keratoses, can show a microscopic picture of a carcinoma-like acanthoma, either in a pure form or with resemblance to seborrheic keratoses somewhere in the section.

In the sections of seborrheic keratoses which we studied, instances of anaplasia, whorls, swirls and pearls of prickle cells, in most type of seborrheic keratoses were found not infrequently—associated with marked inflammatory cell infiltrate in cutis, and edema, and parakeratosis in the epidermis.

In addition, eight sections were found, with areas of acanthomatous change, and with typical seborrheic keratosis configuration in immediately adjacent areas, and in which inflammatory changes were either not marked or minimal. (Figures 5, 6 and 7) The clinical diagnoses of these eight sections were:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Approx. Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrheic keratosis</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Nevus</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Verruca vulgaris vs. cutaneous horn</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

It is not unlikely that Sutton and Sutton's "squamous cell keratoses", could be grouped with these sections.
Fig. 5. This lesion occurred on the left cheek of a fifty-two year old white female, and was taken for a verruca vulgaris or cutaneous horn clinically. The left hand portion of the section is typical of seborrheic keratosis, while the part on the right displays acanthomatous change, with little accompanying inflammation.

Fig. 6. This was a lesion of twenty-five years' duration on the abdomen of a fifty year old white female. It had bled and turned darker, eight months before removal. It presents an acanthomatous appearance, without accompanying inflammation.
Thus, in none of our two hundred and forty-six seborrheic keratoses examined by biopsy, was there any real clinical evidence of malignant transformation, nor was there any microscopic evidence of change except to the carcinoma-like acanthoma we are discussing and this change occurred both with and without accompanying inflammation.

During the course of this investigation, the opportunity presented itself to follow and observe three patients clinically and to obtain repeat biopsies from the same lesion in these cases.

The first patient was a seventy year old white male. He complained of a lesion on the posterior aspect of the left thigh, of two months’ duration, which had bled recently. Clinically, this was a keratotic papular lesion with angiomatous elements, and was thought to be malignant. About one quarter of the papule was removed by punch for biopsy. (Figures 8 and 9) The resultant bleeding was permitted to stop spontaneously, so as to preserve the rest of the papule intact. The lesion was then observed for three months, during which time it changed very little and remained erythematous and verrucoid, much as it had been when first observed. At the end of this time, it was removed completely for biopsy. (Figure 10) Both sections presented a similar picture, that of our acanthoma, with no greater apparent malignant trend in the second than in the first.

The second patient was a thirty-six year old white man. He presented a lesion on the left thigh of six months’ duration. Clinically, this too was a keratotic
Fig. 8. This section is from the first biopsy of the angiomatous keratotic papule on the posterior aspect of the left thigh of a seventy year old white male. Most of the papule was preserved for observation.

Fig. 9. A higher power view of part of Figure 8. Prickle cell whorls, teleangiectasia and edema may be seen.
Fig. 10. This is a section from the remainder of the papule sectioned and pictured in Figures 8 and 9. This biopsy was taken three months after the first one. Acanthomatous hyperplasia of prickle cells with pearls and whorls, and edema and teleangiectasia are well developed.

papular lesion, but the immediately adjacent smooth flat skin was light brown. It was suggestive of malignant epithelial tumor, with inflammatory changes. A small portion of this papule was removed by punch for biopsy and the rest of the lesion maintained intact as before. (Figures 11 and 12.) This section showed the pearls and whorls of our acanthoma. Three months later, the lesion had become smaller and flatter, and resembled a seborrheic keratosis, and was removed completely for biopsy. This final biopsy showed the network-like epithelial proliferation of a typical seborrheic verruca, with inflammatory cell infiltrate.

The third patient was a forty-three year old white woman who presented a lesion of two months’ duration on the anterior aspect of the right leg. This was a lesion about one inch in diameter, and was considered a possible but atypical seborrheic keratosis, or an intra-epidermal carcinoma. A biopsy specimen was taken and was reported as a seborrheic verruca by our general pathologist. Actually, the microscopic picture was that of the serrated variety of seborrheic keratosis first described by Becker, and belonged with one of the groups that comprised a sizable proportion of the sections of seborrheic keratoses that we studied. Because this type of seborrheic keratosis was not familiar to us at the time, and we were not fully in accord with the pathologic diagnosis offered, the lesion was preserved for clinical observation.
It had been present six months. A small portion of this lesion was removed for biopsy and the remainder observed for three months. At the end of this period of observation, this remainder of the original lesion was removed completely for biopsy. At this time, both clinically and histopathologically the lesion resembled a seborrheic keratosis.

Six months later, the lesion showed mica-like scaling, and an erythematous base, and was re-examined microscopically. This section could be classified with our acanthoma. Six months later, the lesion had lost its erythema and appeared as an almost skin colored maculopapular area with a small amount of yellowish scale.

A third and final biopsy specimen was taken at this time, and the histologic picture was found similar to that of the first biopsy. The final examination was made two years after the first biopsy. In all, about one-third of the original lesion had been removed by punch for biopsy and care had been taken to preserve the rest of the lesion, as in the other cases. The remaining two-thirds of this lesion, on final examination, had undergone spontaneous complete involution, leaving normal skin.

Clinically, two of these cases were keratotic papular lesions with angiomatous elements, similar to the four lesions listed in Tables I and II which included Weidman’s and Kreibech’s cases. In one of these cases there was no change towards malignant appearance in a three-month interval, by usual histopathologic standards. The other case showed reversion to a seborrheic keratosis with an inflammatory cellular infiltrate.
FIG. 12. A higher power view of part of Figure 11, showing the features of pseudo-epitheliomatous hyperplasia (Weidman) as described before.

The remaining case, clinically, presented a verrucous seborrheic keratosis or perhaps a senile keratosis. From the microscopic sequence, however, this started and ended as a serrated seborrheic keratosis, with one biopsy specimen in between resembling the acanthoma we have been discussing. Finally, it underwent complete involution, leaving normal skin.

SUMMARY AND CONCLUSIONS

Seborrheic keratoses generally are considered to present no difficulty in diagnosis either clinically or microscopically.

However, a surprisingly large percentage of those having microscopic studies have been misdiagnosed clinically as pigmented nevi, basal cell carcinomas, angiomatous keratotic papules resembling pyogenic granulomas, melanomas and other entities.

In most instances, the microscopic appearance of these misdiagnosed lesions is sufficiently suggestive of the usual picture of seborrheic keratoses to give no further difficulty.

Occasionally however, lesions clinically seborrheic keratoses, or resembling one of the above described variations, will show no resemblance to a seborrheic keratosis microscopically, but will rather closely resemble a prickle cell carcinoma, with whorls, swirls and pearls of prickle cells.

Through repeat biopsy studies on the same lesions in three patients, and
through indirect studies from the literature, and from a study of many sections of seborrheic keratosis in our clinical files, evidence is offered that these clinical and microscopic variations are not malignant, but are instances of "pseudo-epitheliomatous hyperplasia" (Weidman) in seborrheic keratoses.

It would also appear likely that many or most of the instances of supposed cancer arising in seborrheic keratoses reported in the literature, including Sutton and Sutton's "squamous cell keratoses", were cases of "pseudo-epitheliomatous hyperplasia" (Weidman) in seborrheic keratoses.

In our studies such hyperplasia was found with and without marked inflammatory changes, and it occurred also in one instance of dilated pore (Winer).

No unequivocal evidence was found to indicate that seborrheic keratoses ever give rise to actual cancer whether of the basal, squamous or mixed types.

ACKNOWLEDGMENTS

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REFERENCES

1. Protocol of the histopathologic section of the American Academy of Dermatology and Syphilology meeting in Chicago, December 9, 1953.