THE LINGUAL MANIFESTATIONS OF ANIACINOSIS, WITH ESPECIAL CONSIDERATION OF THE DETECTION OF EARLY CHANGES BY BIOMICROSCOPY.[1,2,3]

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IN previous papers we have described methods for detecting ariboflavinosis and avitaminosis A by gross and biomicroscopic examination of the limbus and conjunctiva, respectively (1, 2, 3). This paper presents a preliminary report of observations on changes in the tongue in aniacinosis (nicotinic acid deficiency or disturbance) as seen in the gross and with the biomicroscope. The number of cases was sufficiently large to show all states of the lesions.

Following administration of nicotinamide as specific therapy, the tongue lesions in three persons have now almost completely disappeared, as judged by microscopic examination. Initially more severe, the lingual lesions in all twelve others under this therapy have markedly receded, in some nearly completely. These persons are still receiving the specific therapy, and their lingual manifestations are continuing to undergo recession. Control groups receiving ascorbic acid or vitamin A have had no improvement of their lingual lesions.

Gross and biomicroscopic examination of the tongue is an advantageous method of detecting all states of aniacinosis.

DESCRIPTION OF GROUPS AND PROCEDURES

Forty-nine adults, 19 to 46 years of age, were examined. Twenty-three of the persons were white females; three, colored females; and twenty-three, white males. The white individuals were from

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various racial stocks. None regarded himself as sick, and all attended work regularly. All except four received wages ranging from $69-95 a month; four received over $100 a month.

Their tongues were examined, prior to therapy, with the biomicroscope as well as in the gross. Both types of examination were conducted on the anterior three-fourths of the surface of the dorsum and edges.

Likewise, their gums in their labial aspect were examined grossly and microscopically; the angle of the mouth only grossly. Inasmuch as specific skin lesions have been traditionally regarded as an early manifestation of aniacinosis, the skin was examined, prior to therapy, in all persons with all grades of severity of lingual lesions.

Seventeen persons were selected at random to receive nicotinamide therapy. They presented various states of tongue lesions. The remainder, forming a control group, were given ascorbic acid.[4] Another group, receiving vitamin A, served as an additional control group.

The specific daily therapy, started on April 9, 1941, consisted of 200 mg. of nicotinamide in four tablets of 50 mg., each being given at an interval during the day. During the five work days, the therapy was taken in the presence of the dispenser; for over the week-end a supply was given to be taken home. None of the individuals was advised of the nature of his lingual condition. There was no suggestion to take other therapy, or to modify dietary habits.

The daily dosages of ascorbic acid and vitamin A for the control groups were 500 mg. and 100,000 I.U., respectively.

Among those receiving the nicotinamide therapy, two have since become unavailable through departure and could not be further followed. For similar reasons, seven from the control group had to withdraw. At regular intervals tongue examinations have been con-

[4] The ascorbic acid given to the control group was generously furnished by Mead Johnson & Company, Evansville, Indiana.

ducted on the groups receiving the specific and control therapy, respectively. For the former, these examinations will form the basis for terminating therapy.

Description of Lingual Manifestations

In the evolution and recession of its specific lesions, aniacinosis was seen to be similar in behavior to avitaminosis A (3), avitaminosis C (4), and ariboflavinosis (5). While each has its individuality as a separate and specific entity, all four avitaminoses have several characteristics in common. They reflect a definite, biological pattern. From this was elaborated the concept of deficiency states presented in the preceding paper (6).

There it was shown that in a deficiency disease the specific pathological process in a tissue is characterized by velocity, intensity, and sequence. Of the velocities occurring, the range may be classified into two principal categories, which are subdivided. The acute process is rapid in appearing, in running its course, and in responding to therapy. Somewhat less rapid is the subacute or mild acute process. Differing from these in velocity, the chronic process is slow in onset, progress, and response to therapy. Even slower is the mild chronic process.

Since the pathological process may be of any intensity, it is convenient to graduate the range in two degrees, mild and severe. Therefore, the acute and the chronic process may be either mild or severe. With grouping by form and intensity, the simplest classification of processes provides the categories: mild acute, mild chronic, severe acute, and severe chronic. These are the same groups that were enumerated in designating a process according to its velocity. Hence, the mild and severe states are seen to differ in velocity as well as in intensity.

If uninterrupted, the process manifests its changes in a definite sequence which may be divided into stages. Therefore, in each of the categories, it may be divided into stages.

Through the common vicissitudes, particularly over years, the process usually changes in velocity, intensity, and even direction. Most common of the eventualities, the mild or severe chronic state, once contracted, constitutes a base on which is superimposed a mild or severe acute state.

We have devised a system of appraising the condition of the tongue in aniacinosis which takes into account the form, intensity, and stage of the pathological process. First, it may tentatively be classified according to the two main categories: acute and chronic. Then from its degree, it may be characterized in intensity as well as more closely in form. Finally, its stage is identified. Actually, this system provides more and finer divisions of intensity than just mild or severe. For both the acute and chronic processes, intensity is gauged in three degrees. The resulting acute forms are divided into four successive stages, the chronic into five, each with its particular and identifiable characteristics. A stage may show features of the preceding and next phase, but it is judged by its predominant characteristics.

In using this system, the status of the process may be most readily judged by visualizing its position on the graph presented in the preceding paper. If acute and chronic processes are both present—as most frequently they are—they can be appraised separately according to their intensity and stage. From two coordinates, degree and time, the position of each in its respective zone may be located as a point. Status is designated by a combined dual rating.

In the present series of cases the tongue as a whole, as well as its elements, the filiform and fungiform papillae, showed changes. Some showed marked gross manifestations; others exhibited less pronounced but unmistakable gross changes; a few, exhibiting very little grossly, displayed definite alterations perceptible by biomicroscope. All forms and gradations in degrees, stages, and extent of the pathological process were represented, except the advanced stages of the severe acute type. Both by arranging them in a progressive

series and by interpreting the reverse sequence of changes upon therapy, the details in the pattern of the pathogenesis could be reconstructed and the course of events determined.

In the tongue and its papillae, various pathological changes appear in definite sequence. However, it should be emphasized that here sequence refers to appearance and that inasmuch as a succeeding manifestation emerges long before the preceding one has disappeared, both may be present concurrently. In the acute forms, vascular hyperemia and proliferation, hypertrophy, and then extinction occur successively in the papillae. The vascularity and hypertrophy of the fungiform papillae impart to the tongue the familiar stippled, then the strawberry aspect, depending on the degree and stage. Redness and swelling, marginal indentation, and then baldness manifest themselves in the tongue. In the chronic form, the stages of progression in the papillae are: vascular hyperemia and proliferation; infiltration; and atrophy. As the chronic process advances, the tongue itself shows fissures, crevices, and loss of substance, producing generally a thin tongue with marginal serrations. Usually, there is a preferential order of involvement of the two kinds of papillae: the fungiform precede the filiform in undergoing change.

Each stage of the pathological process manifests an intensity and extent corresponding to the degree of the cause. But it should also be cited that the same stage may not prevail over all the tongue; different sites may show different stages. Although the changes in each part follow the same pathological sequence, all parts may not be synchronously affected.

Instead, the regions tend to be affected in the following definite order: tip, anterior and antero-lateral edges, anterior and antero-lateral margins of the dorsum, anterior border of predominantly filiform zone, mid-dorsum. Considering that the fungiform and filiform papillae differ in their distribution over the tongue, it is seen that regions with the same predominant type do not undergo simultaneous change. In general, involvement appears first an-

teriorly and proceeds posteriorly. It is of particular significance to note the extent to which involvement has advanced; the extent of the predominant stage of the process; and the extent of the most advanced stage.

In presenting in some detail the sequence of pathological changes in both the acute and chronic processes, we will follow the arbitrary divisions of the rating scheme and describe the characteristics of the successive stages.

In the acute state fungiform papillae are red from their vascular proliferation, dilatation, and engorgement. To a lesser extent the same reaction is present in the filiform papillae, but their opaque tips mask most of the vascularity. With them as a background, the injected fungiform papillae impart to the tongue a stippled appearance. These changes range in degree from slight to marked: they are the more intense, the more pronounced the causal agency. Similarly, the extent of the affected area depends on the degree of the cause. The hyperemia appears in the papillae at the edges of the tongue and proceeds over the margins.

Then swelling, in addition to the redness, of the papillae appears. These changes may be restricted to the tip and margins of the tongue. Here the reddened and hypertrophic papillae may stand out conspicuously. In marked degree the papillae may become much enlarged.

Next the tongue itself shows redness and hypertrophy. If the process is mild or moderate, the tongue is covered in the middle, but red and smooth on the tip and margins. Although the present series of cases contained none of severe intensity in this stage, the picture has been repeatedly seen and recorded in acute pellagra. If the process is markedly intense, the tongue, deeply injected and deprived of its papillae, is red and smooth, a cardinal or bald tongue. It may be quite large from swelling and show the identations of the teeth.

Ulcers or erosions may occur on the tongue late in the process.

Usually they begin on the edges and may later appear on any portion of the tongue surface.

In the chronic state the first stage presents redness and swelling in the fungiform papillae. These manifestations are in proportion to the degree of the cause.

In the next stage these papillae are likewise hypertrophied. But as a distinctive feature they show beginning infiltration which partially obscures their vessels and thereby diminishes their redness. In the mild state the size of the fungiform papillae is only slightly increased. All the filiform papillae are present on the dorsum except where a small atrophic spot may be seen.

In marked degree the tongue is very thick and may have a slight yellowish cast. Everywhere the fungiform papillae are markedly hypertrophied, with marked infiltration masking the hyperemia. On the lateral margins the few fungiform present may be yellow. Some may be seen ruptured with their yellow contents released.

On the dorsum the filiform are also markedly hypertrophied. Both kinds of papillae are so similar in appearance—in size, shape, and color—that they may scarcely be differentiated. Elsewhere the filiform papillae may be entirely absent. Here and there are very small atrophic spaces which probably mark their previous site.

Late in this stage, the tongue with a mild degree of involvement may present the following additional changes: On the anterior edge at the midline the fungiform papillae are embedded; elsewhere on the edge they are hypertrophied, but less than on the dorsum. At the midpoint of the anterior edge and front part of the anterior margin the tongue is smooth because the fungiform papillae are embedded. Elsewhere on the edge and margin they may be partially embedded. Then the upper part of each papilla projects as a small mound above the surface; the remainder is embedded.

On the anterior dorsum the filiform papillae may appear as small hobnails with small nests of atrophic fusion. Or they may

show partial or complete fusion and atrophy. On the anterior margin they may be reduced in number by 50 per cent or more. Then they are slender, show only a little cornification at the tip and project only slightly above the surface. On the anterior edge few or no filiform papillae are present.

In slight degree there may be a small seemingly eroded spot in the midline at the anterior border of the filiform zone, where these papillae have undergone much atrophy or completely disappeared. It may also appear mid-dorsally. Or, extending down the midline of the dorsum is a slight longitudinal fissure. On its walls are several white hypertrophied fungiform papillae. Dorsally the longitudinal fissure terminates in a transverse fissure. In high degree, there may be multiple slight crevices containing a few fungiform papillae in bullous form. All these changes represent the beginning of the next stage.

In stage 3 the infiltration in the fungiform papillae may be complete, so that it masks their vascularity. Indeed, they appear almost or entirely white. Another distinguishing feature is a longitudinal fissure extending down the midline and usually containing several bullous fungiform papillae. Scattered crevices may also be seen on the tongue. Furthermore, on the dorsum the slightly hypertrophic filiform, without fimbriation or cornification, are not easily distinguishable from the fungiform papillae.

Fungiform papillae on the dorsum are much less hypertrophied in this than in the preceding stage. Their previous hypertrophy seems to have given way to beginning atrophy. On the edges of the tongue they are much flattened or completely embedded. Filiform papillae are missing, for the most part, from the anterior edge and margin.

In the higher degrees of this stage the same relationships prevail but all the manifestations are more pronounced. On the anterior margin many of the fungiform papillae have become spatulate in form. Marked infiltration veils much of their vascularity. More and

deeper longitudinal fissures are present. The deepest runs along the midline and may bifurcate the tongue at the tip to produce the so-called swallow-tailed tongue. The other fissures may be parallel to this. On the walls of the fissures may be seen bullous or spinous papillae which were once fungiform.

Few or no filiform papillae are on the anterior edge and margin. They are present on the dorsum and have increased diameters but less projection. In appearance they are quite similar to the fungiform in this stage.

Late in this stage, both kinds of papillae have undergone further change. In the low-degree tongue, linear groups of two or more markedly infiltrated fungiform papillae have united to form cords on the anterior margin. Filiform papillae on the dorsum present a mixed picture. In one area they may be slightly hypertrophic; in another they may show atrophic foci with fusion of two to six papillae. More frequently there are broad areas of marked fusion and atrophy.

In the high-degree tongue, the previously hypertrophied papillae on the anterior margin of the tongue have atrophied to their original size. These heavily infiltrated papillae have a distinct outline but are deeply embedded. Still later they are markedly fused. These changes also extend to all fungiform papillae on the dorsum. Likewise, the previously hypertrophied filiform papillae on the dorsum undergo still further atrophy. They are partially fused and project so little that the surface of the tongue approaches smoothness. These changes usher in the next stage.

In stage 4 atrophy of the papillae tends toward extensiveness and completeness. Consequently, the tongue becomes denuded and smooth. It becomes thinner, probably through loss of substance in the broad sense of the word. Any previous fissures diminish and disappear. The tongue becomes whitish, often with a yellow cast. There may also be heavy furring over the tongue.

On most of the dorsum the filiform papillae may be partially

atrophied and fused, but in scattered foci or small areas they may be completely fused. Complete atrophy usually occurs in a wide sector along the midline. This latter forms a low region. Or there may be complete atrophic fusion and flattening over the entire dorsum, forming a large depressed area. Near the lateral margins there may be narrow band-like areas of partially fused, slightly projecting filiform papillae.

On the anterior margin the fungiform papillae are variable. In some tongues they may not have reached the atrophic state. In others they may be only slightly atrophic. Or throughout the area they may be flat and not sharply discrete. They may also be embedded to such an extent that the surface is nearly smooth. There may be foci of markedly atrophic and almost completely fused papillae. Only a few filiform may be present. These are isolated islets of disorganized, fused, atrophic papillae. Or they may be absent. Then the zone may be so completely atrophied in certain foci that it is impossible to distinguish the type of papillae. Thus, the surface of the tongue tends to become denuded and smooth.

As areas of depression appear centrally on the tongue, fissures from the previous stage diminish and finally disappear. Hence, some tongues may show residual shallow fissures. The entire tongue is perceptibly thinner and less red than in the preceding stages. It may have a yellow cast or a heavy coat.

At the lateral edges some tongues may show loss of substance indicative of the next stage.

In stage 5 the same type of manifestations as in the preceding stage is seen, but the atrophic process has proceeded further. The lateral edges are thin or have eroded areas. By early workers the latter were called slashed edges. In some, this may amount to a considerable loss of substance. The entire tongue is thin, smooth, and white.

The fungiform papillae are embedded, in some instances fused, except in the mid-dorsum where a scattered few may be spinous in

shape and project strikingly above the smooth surface of the thin tongue.

It should be reiterated that an acute process may be superimposed on a chronic base in any stage. For example, a thin, smooth tongue with thinned and eroded lateral edges may become red and have hypertrophied fungiform papillae project mound-like above the surface on the anterior margin and mid-dorsum.

None of the persons showed any cheilosis or skin lesion.

Changes on Therapy

Upon administration of the nicotinamide daily there was recession of the acute and then the chronic process. The severe advanced acute stage of pellagra is known to subside rather rapidly. As might be expected where the acute was superimposed on a chronic process, the former disappeared first. Redness and swelling of the tongue and papillary hypertrophy diminished and disappeared before the chronic changes underwent substantial reversal.

Then occurred recession of the chronic lesions in reverse sequence of their pathogenesis. Thus, they receded in definite order: lessening, then disappearance of atrophy, fissures, and infiltration. Naturally, in any instance, the stage of the chronic lesion determines the nature and site of the first changes in repair. It is not unlikely that in tongues with severe chronic lesions, repair in each of the several pathological manifestations may be operating simultaneously. But cessation of the most recent manifestation may at first be the only one observable. Because the manifestations appearing early in pathogenesis have more pronounced and extensive development, their recession may at first be relatively so slight as to be unobservable. The response of the various stages to therapy may be described in a composite account.

The tongue in the advanced stages of the chronic process became thicker, possibly by regaining vascularity, tissue substance, and fluid. The rodent areas along the lateral edges filled. Furring, discoloration, and smoothness on the surface disappeared.

On the dorsum, the filiform papillae which were previously indistinct and atrophic began to reappear in small numbers. Later they appeared over the entire area and became somewhat discrete, though at first they did not project very much above the surface. Thus, they gradually resumed their orderly arrangement. Still later they returned further to their usual shape and projected somewhat more above the surface. With the process, depressed areas or sectors filled. Also, the restoration of the papillae covered any denuded surface.

On the anterior dorsum, the fungiform papillae which had previously been partially or completely embedded began to project above the surface. Those which had been white now showed redness due to resorption of the infiltrate. Fungiform papillae which had been hypertrophied now diminished in size. At this point the filiform papillae on the anterior margin might still be completely fused. Often the filiform papillae in and adjacent to the area occupied by the fungiform were the last to show recovery, particularly if the fungiform were hypertrophied.

Fissures, especially prominent in stage 3, began to fill. Bullous papillae on their walls diminished and disappeared. Atrophic sectors or spots flanking the course of the fissures showed increased discreteness of the filiform papillae. After one year's therapy some fissures as well as most crevices already have entirely disappeared.

Elsewhere in this stage the hypertrophied fungiform and filiform, previously so similar in appearance, rather soon began to return to their usual dissimilarity. Resorption of the infiltrated material in both removed much of their hypertrophy and left the reddish fungiform in sharp contrast with the gray filiform papillae. Consequently, they could again be readily differentiated.

Tongues in the earlier stages showed the following response to therapy: In all zones the hypertrophied fungiform papillae diminished in size and assumed a reddish tint due to withdrawal of infiltrate. In atrophic areas on the dorsum, filiform papillae reappeared,

at first with slight, later with more discreteness and projection. Small areas near the anterior margin were usually the last foci to have the filiform papillae restored.

It should be noted that the criteria of complete recovery are rigorous since they are based on microscopic observations. After receiving therapy for fourteen months, three persons with their tongues showing almost complete restoration are near discharge. Several more are not far from complete recovery and discharge; all others have shown very marked improvement. In every instance the point to which the tongue has receded is in proportion to its stage before therapy. Naturally, the less advanced are among the first to show complete recovery. Nevertheless, they have required more than a year's intensive therapy.

Control groups receiving ascorbic acid or vitamin A have shown no improvement in their tongues.

Following the full recovery of those still receiving nicotinamide therapy, there will be a further report.

Discussion

Since pellagra results from a deficiency or disturbance in nicotinic acid, it is natural to ask what is the relation of the tongue changes to the disease. To find the answer it is helpful to trace the gradual change in views on the pathogenesis and diagnosis of pellagra. Then, through the concept of deficiency diseases and their detection, we may place tongue changes and pellagra in their proper positions and perceive their relationship.

Pellagra is a deficiency disease characterized by gastrointestinal disturbances, skin lesions, and sometimes neurological and mental manifestations. To the early investigator the disease showed so many manifestations and seemed so varied in evolution that it presented difficulties in characterizing its components. Each could be predominant. It was debated whether these many manifestations represent several types of pellagra or several stages of one type.

Lombroso wrote about types of pellagra, designating each by its predominant manifestation (7). Procopiu also classified pellagra into types according to the prevailing signs (8).

By almost all others, however, pellagra was recognized as an entity, though its manifestations were not restricted to one organ or system. Diverse systems were involved; not all were affected simultaneously, nor with the same intensity. Consequently, much discussion centered on whether pellagra developed in a definite and orderly progression, whether its several manifestations appeared in sequence. If so, the disease could be divided into stages based upon the predominant manifestations.

On this, there was much difference of opinion. Frapolli was the first to advocate division of pellagra into stages (9). Others subscribed to the validity of stages but suggested different divisions of the manifestations (10-15). Strambio based his stages not on predominant manifestations, but on the persistence or recurrence and the severity of the disease (16). More properly his stages should have been designated forms and degrees.

Others objected to division of pellagra into stages. Lombroso regarded it as artificial and inaccurate (7). Marie (17) asserted: "... the evolution of pellagra in a given case is not so logical as to have one stage succeed another. In a general way, it may be affirmed that the so-called first stage has reference to the gastro-intestinal and skin symptoms; ... As a rule, pellagra is a chronic affection and the duration of each stage is indefinite. Furthermore, the line of demarcation is not well defined between the different stages."

Roussel, whose writings on the evolution of pellagra are classic, concurred in this (18). In his opinion, the infinite variety in the course, duration, and gravity of individual cases vitiated all attempts to measure the progression of pellagra by phases, periods, or stages.

Several investigators divided pellagra into degrees according to its intensity (19-21). Roussel adopted the system of classification

into degrees but on a basis that only in part pertained to intensity (18). Despite his objection to dividing the disease into stages, his system of degrees was founded on the sequence of manifestations and grouping according to the predominant signs. Actually, his degrees were largely stages.

Commenting on the several systems of classification, Cazenave and Schedel (22) wrote: "The division of pellagra into commencing, confirmed and inveterate, is not a practical one, for pellagra may be beyond hope from its commencement. The expressions period or degree, which convey the idea of certain fixed symptoms and appearances, are not adapted to the description of a disease so capricious as pellagra. The term degree seems to indicate an increasing intensity; while the second or third time of appearance of the disease may be less severe than the first. When we employ these terms, therefore, we shall use them only as symptoms of a more or less advanced step of the disease; for, like every other disease, pellagra has a beginning, a progress, and a termination."

It may now be seen that all the classifications were open to criticism. Terms were used loosely or synonymously; they would indicate one basis of classification when another was actually used. Very often the system of classification was on a mixed basis. None was sufficiently comprehensive. They would have division on the basis of intensity to the neglect of stage, or vice versa.

The difficulty of the early workers in evolving a satisfactory method of classifying the various manifestations into stages is understandable. Their mistaken view on the etiology of pellagra colored their view on its nature and course. Many looked upon pellagra as a toxic disease and they expected it to fit that pattern. At that time they could not know that pellagra was a deficiency disease which may have a course very variable and quite different from that of a toxic or infectious disease.

Whether they sought to distinguish stages or degrees, all wanted to know the course of pellagra. They wished to recognize its se-

quence in order to know how far advanced were particular states. They also wished to know the earliest stage and its characteristics. Many systems of classification into stages or degrees included a prodromal period or an incipient pellagra (9, 10, 11, 13-15, 18, 23, 24). Even as early as 1866 Roussel, in mentioning his interest in early diagnosis, stressed the importance of discovering the site of initial change (18).

How many and what signs are necessary for diagnosis of pellagra was a topic under consideration even at that time. For all signs to appear, the disease would have to run its entire course. But, obviously for early diagnosis, all signs cannot be expected. That inescapable conclusion raised several kindred questions. How far must the process have developed before diagnosis may be safely made? How early may it be detected? What are the first valid signs? Roussel's distinction between the beginning and confirmed states, his use of the term confirmed, and his implicit acknowledgment that skin lesions were necessary to confirm the diagnosis, foreshadowed the trend in attitude which has since prevailed.

Perhaps because skin lesions were so prominent, they came to occupy the principal place among the signs. While other features were recognized, the dermatitis was given such weight as to overshadow them. It even preempted the name of the disease. Its presence was regarded as necessary for diagnosis. After it had become the decisive diagnostic factor, it alone was soon regarded as sufficient for diagnosis, and as the first reliable, valid sign.

Yet, several investigators have stated specifically that first changes do not occur in the skin; that other manifestations precede (12, 13, 15-18, 24-27). Indeed skin changes may be absent in pellagra, as was noted under the paradoxical term pellagra sine pellagra (7, 8, 16, 28). Sandwith (24) wrote: "The skin eruptions, although the least important of the various symptoms, have given the disease its name, and have always received an undue amount of attention."

Several experiments on exposing various parts of the body to the

sun while protecting other parts (19, 29, 30) suggest the circumstances under which the cutaneous lesions appear. Lavinder and Babcock (17), summarizing this, write: ". . . granting that the exanthem may . . . develop more slowly, the skin is none the less affected in the shade, but sunlight intensifies the eruption, and it is not to be denied that the rays of the sun are thus an exciting cause of the skin lesions. . . ." Perhaps, like night blindness in avitaminosis A, skin changes in pellagra are provoked, aggravated, or exaggerated by light, although they would emerge later spontaneously.

In any event, dermatitis is not the first change; indeed, it may not be present. It is not a *sine qua non* for diagnosis; certainly it is not a constant and reliable sign for early diagnosis. Nevertheless, dermatitis has remained unduly emphasized and in its absence many refuse to diagnose pellagra.

Several investigators have stated that beginning pellagra is characterized by gastrointestinal disturbances (8, 12, 13, 15, 18, 23, 24, 27), and the first observable tissue change is in the tongue (12, 15, 18, 25, 26, 27). Accordingly, it may well be asked: Can aniacinosis be appraised by changes in the tongue? Are specific changes in the tongue indicative of pellagra? Can early or mild pellagra be diagnosed by this specific glossitis alone? What is the relation of pellagra to aniacinosis?

For usefulness in the recognition of early pellagra and aniacinosis, any sign must meet certain criteria. It must always occur, be specific, and appear early. Since it is necessary to detect aniacinosis in all forms, degrees, and stages, and it is most convenient to use one manifestation which reflects all these, it is essential that the sign not only appears early, but persists and changes in proportion to the progress of the disease. It must be readily accessible to demonstration, preferably by an objective method.

By its never-failing occurrence in human pellagra, glossitis was shown to be a reliable sign. Even those who did not regard it as the

first sign, mentioned its presence. Furthermore, glossitis has been produced in experimental animals on B complex (31) or nicotinic acid-deficient (32-36) diets. Both the experimentally-induced glossitis in animals (37-39) and naturally-occurring glossitis in human pellagrins (40-42) have been cured by nicotinic acid. Moreover, in the last decade numerous endemics of glossitis, with or without angular stomatitis, have been reported (43-51). Gradually, the nature of the specific deficiency responsible for the occurrence of the glossitis was identified, as yeast (48-49) autoclaved yeast (50, 51) autoclaved alkaline yeast (52) and finally nicotinic acid (53, 54) were found to improve and cure it. From these lines of evidence, glossitis is seen to be a specific sign of pellagra and aniacinosis.

As the earliest presenting tissue change in pellagra, glossitis has been repeatedly reported in the past (12, 15, 18, 25, 26, 27). More recently it has likewise been recognized as the earliest discernible tissue manifestation (55-56). The occurrence of endemic glossitis further attests to its priority (43-51). The prevalence of tongue changes in the present series, with absence of other signs of aniacinosis, furnishes additional evidence. All this is not to say that glossitis is the first change in the body in pellagra and aniacinosis. Rather, among the readily observable objective signs, it is early, if not the earliest.

There has been some question whether the early specific changes in the tongue are indicative of pellagra. Its corollary is the question whether early or mild pellagra can be diagnosed by the specific glossitis. Among many clinicians, admitting that skin lesions were not first, strong tradition has made them reluctant to make a diagnosis of pellagra until skin lesions have appeared. Most of those who agreed that the first observable tissue change is in the tongue, skirted the issue by stating that this change characterized latent, prodromal, or beginning pellagra (15, 18, 26, 27). Even yet the person with typical tongue changes is not said to have pellagra. The matter is circumvented by calling glossitis a "pellagrous tongue," or

a sign of prepellagra (56). Quite general is the attempt to preserve the historical conception and designation of pellagra in contradistinction to its earlier states. Actually, however, they are only different states of one and the same process.

Perhaps the concept presented in the preceding paper (6) may help to locate the place of pellagra in aniacinosis. There it was shown by the simplest classification, a deficiency disease may exist in any one of the following states: mild acute, severe acute, mild chronic, severe chronic, as well as mild or severe acute superimposed on mild or severe chronic, each in a particular stage. It may be seen that aniacinosis, arising from deficiency of nicotinic acid, or of a chemically related compound that is its biological equivalent, or from disturbance of its metabolism in bodily tissue, covers all forms, degrees, and stages. Pellagra represents the severe degree and advanced stage of the acute form. This concept helps to relate the various manifestations in the tongue to respective states of aniacinosis; to clarify events in the ofttimes tortuous course of aniacinosis; and to emphasize the different rates of response to therapy according to the forms.

Most of the literature on pellagra is on its acute severe form. In these accounts the nature and sequence of tongue changes in acute pellagra have been abundantly reported. But it should be borne in mind that the acute severe form of aniacinosis may be engrafted on a mild or severe chronic base. Careful examination indicates that some manifestations of the tongue attributed to the acute state are actually characteristic of the chronic state. Either the acute process in the tongue was becoming chronic or, more likely, an exacerbation arose on a chronic base.

Pellagra has been called a chronic disease (8, 17) because its onset was often lengthy and its long course was punctuated by periodic and recurrent exacerbations. Several other investigators mentioned a chronic state, in contradistinction to the more dramatic acute form (11, 16, 57, 58). Relatively, however, chronic pellagra as a

distinct form has had little recognition. Some changes in the tongue have been described erroneously as part of the acute process, whereas they are really chronic in nature. Soler (59) and Lussana (13) mentioned fissures and coated tongue. Others cited furrows, smoothness, and yellow coloration (7, 18, 60).

In a notable paper emphasizing the importance of the tongue in diagnosis of pellagra, Gemma in 1872 wrote a comprehensive and detailed description of the lingual changes in pellagra (25). He described characteristics of the various lesions and tried to relate them in succession. Most of his affected persons, however, had acute changes on a chronic base. Since he drew no distinction between the acute and chronic forms with their respective manifestations, the sequence of changes which he recorded bears revision. Nevertheless, his characterizations of the tongue lesions are superb; most of them were seen in the present study; and much that he says about them, particularly his descriptions of the tongue in the course of the disease, and in the "cured" or arrested state, and in supposedly well adults and children, can be interpreted in the light of present work. It is significant that he noted the similarity between certain pellagrous and so-called senile changes in the tongue.

In the past some attention has been given to mild acute pellagra and its tongue changes. But the mild chronic state has gone almost entirely unrecognized. The lingual changes in the mild and severe states are similar except in degree. The most common states, acute with chronic, have not been fully appreciated as such and have not had their two constituent forms distinguished and separated. The present work supplies information on these forms, stages, and degrees as well as on the severe states. All the evidence indicates that tongue changes are present in all states of aniacinosis.

Two further points bear upon the recognition of the various states in relation to criteria and length of time for complete therapy. Many descriptions of pellagra have stressed its tendency to recurrence and periodicity (7, 8, 10). It is not unlikely that these pheno-

mena are associated with its chronicity. Usually relief of symptoms or clearing of skin lesions has, in the past, been regarded as the index of complete recovery and the signal for termination of therapy. In such a practice, judged by criterion of perfection, recession in the tongue would not be complete and therapy will have been prematurely stopped. The tongue is probably brought to a lower level of intensity to become a chronic base. This chronic base may undergo periodic exacerbation. Actually, recurrence has meant the return, not of aniacinosis, which is already present in a chronic stage, but of acute pellagra. As Katzenellenbogen so appropriately says in his paper on the cure of endemic glossitis (54): "To prevent relapse nicotinic acid must be administered for a long period."

In treating endemic glossitis with nicotinic acid, 50 mg. four to six times a day, Katzenellenbogen (54) noted considerable improvement in twenty-one out of twenty-four persons. With nicotinic acid, Aykroyd, Krishnan, and Passmore (53) observed improvement in sixteen out of twenty-four persons. The unsuccessful instances, though in the minority, are worthy of note. Katzenellenbogen does not mention the length of the therapeutic period for his apparently unimproved patients. When it is considered in the series of Aykroyd, Krishnan, and Passmore that fourteen persons received only maintenance doses and that many received therapy for only one week or less, a few for two weeks, and one who received it for twenty-six days had malaria concurrently, their results are surprisingly favorable. In the light of the present paper, which reveals the long period of therapy that may be necessary, depending on the state of the aniacinosis, it is likely that in both studies the length of the therapeutic period for the unimproved persons was too short. Moreover, in the one study, the dosages could not be considered sufficiently potent. The principle that a long period of therapy is necessary for recession of chronic changes is particularly applicable to the study by Alport, Ghalioungui, and Hanna (61) in which they reported that nicotinic acid was only

slightly effective for a chronic pellagrous process in the tongue. In chronic states, the therapeutic response is slow and a very lengthy period is required for complete recession.

From the preceding paper (6) it will be noted that the concentration of a vitamin in blood changes sooner and much more rapidly than does the tissue state, both in evolution and recession of a deficiency disease. Blood is the labile transport system with its concentration of a vitamin responding rapidly to change in intake. In the initial attack of the deficiency disease, the lowered concentration of the vitamin in the blood would be the first demonstrable change to be followed shortly thereafter by tissue change. For a short time, the tissue would be normal while the blood value would be low. But practically this condition is the least frequent in the general population, and is found mostly in infants and preschool children. Furthermore, it should not be forgotten that the biomicroscopic examination of tissue is exceedingly sensitive in detecting the very early and mild tissue changes, indeed all states.

Once chronic changes have appeared—and this is the most prevalent state—the blood values may be unreliable and misleading. The chronic process in the tissues recedes very slowly. In contrast, blood values shift rapidly in reflecting changes in intake, such as from seasonal or occasional dietary improvement or low potency maintenance tablets now so popular, and may temporarily be moderate or high without demonstrable recession in the existing chronic lesion. Even prolonged adherence to a good diet would not bring appreciable recession in the chronic process, while the blood values would be regarded as satisfactory. In all these instances, the blood values would obviously be misleading.

Examination of the tongue meets the criteria for satisfactory detection of aniacinosis. It is available to objective observation. Its changes are specific and invariable in occurrence. They are present in all states of aniacinosis; they appear early, persist, and reflect its course. They permit rating of any state in terms of form, stage, and

degree. It should be noted that stages were used historically in pellagra entirely differently than here. Then almost all the cases were exceedingly severe and well-advanced with several signs, each from a different system, in evidence; the stages were divided according to the predominant sign. In our rating different affected systems are not used as stages; rather the sequence of changes in one tissue. It is interesting that both Lussana (13) and Gemma (25) asserted that from the tongue alone they could identify the stage of pellagra.

Although very much may usually be seen in the gross, the biomicroscope is useful in detecting tongue changes. Very early stages and mild degrees of the process may be observed. It allows low-grade states, whether prolonged or not, to be detected. The less severe the change and the closer it approaches perfection, the more the microscope is needed.

Considerable evidence shows that there is high prevalence of aniacinosis (62). This is understandable. Relatively few persons have eaten a diet entirely adequate in niacin day after day throughout their life. The older the person, the more opportunity he has had for the dietary lapse. Similarly, any of the manifold deleterious causes contribute to impairment. The tongue shows cumulative changes, an arrested, incompletely receded, or progressive chronic as well as an acute process. Then too, the standard of perfection is very exacting and biomicroscopic detection is very sensitive. It is not surprising, then, that high prevalence of aniacinosis is found.

For complete recovery of chronic aniacinosis a long period of therapy is necessary. The acute form disappears, then the chronic process gradually recedes. In respect to response to therapy, aniacinosis is entirely similar to avitaminosis A, ariboflavinosis, and avitaminosis C.

The prevalence of much chronic aniacinosis, the long period of therapy required for its recession, the practice of treating acute

aniacinosis, including pellagra, for only a short time, all these suggest that in the past these states have not been completely corrected. Customarily, pellagra is treated until skin lesions or distressing symptoms disappear. To be complete the therapy should be continued until the tongue shows no abnormality. If therapy is then withdrawn, as it should be, pellagra will not, of course, be prevented in the future unless the diet remains adequate. But even if proper diet is not taken, complete cure will greatly postpone a recurrence.

The use here of 200 mg. of nicotinamide daily is not to be construed as a recommendation or precedent that this amount is necessary for maximum rapid therapeutic results. It is known that the effective therapeutic dosage for an acute avitaminosis is at least five to six times the maintenance requirement. It may be that a somewhat lesser dosage, but still above the dietary level, would suffice for a chronic avitaminosis, but that is yet to be demonstrated.

Summary

Of forty-nine persons in a low-income group, all had gross or microscopic lingual lesions characteristic of aniacinosis.

Following administration of nicotinamide to fifteen persons in this group, the lingual lesions in three have now almost entirely receded, as judged in all instances by biomicroscopic examination. The initially more severe lesions in the others of the therapeutic group have receded markedly, some nearly completely.

In all cases the striking feature is the very long period of time required for complete recovery, more than a year even with therapy of high potency. The type of pathology makes it understandable. In this respect, aniacinosis is similar to avitaminosis A, avitaminosis C, and ariboflavinosis. This common feature, the slow response, leads to a concept of malnutrition in which the importance of chronicity, as well as mild states, is emphasized.

Those persons receiving vitamin A or ascorbic acid have shown no improvement in the tongue.

For detection of aniacinosis, examination of the tongue is recommended as a simple, convenient, objective method. When biomicroscopic is combined with gross examination, all forms, degrees, and stages of aniacinosis may be noted and graded.

The marked prevalence of aniacinosis is explained.

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