



Journal of Spirochetal and Tick-borne Diseases

Fall/Winter 2001

Volume 8

ORIGINAL ARTICLES

Spirochaetes in Aetiologically Obscure Diseases

C. Lennhoff

Successful Treatment of Erythema Migrans Afzelius

Einar Hollström

Penicillin Treatment of Erythema Chronicum Migrans Afzelius

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Rudolph J. Scrimenti, MD

Lyme Disease Redux: The Legacy of Sven Hellerström

Rudolph J. Scrimenti, MD and Mark Scrimenti

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Editorial

A Historical Perspective of Spirochetal and Tick-borne Diseases

Part II

Ronald F. Schell, PhD and Karen Vanderhoof-Forschner

In the last issue of the Journal (Spring/Summer), we published reprints of important historical articles contributing to the early literature documenting that people around the world have been infected with Lyme disease for more than 100 years.

We continue this historical perspective in this Fall/Winter issue by reprinting articles on the Lyme disease skin condition known as "erythema migrans" (EM). EM is a hallmark of what is known in the United States as "Lyme" disease. However, all the articles discuss the wide variations on a name that have been given to this disease. While first described by A. Afzelius in 1909, these articles show the maturation of scientific knowledge about this disease.

More striking are how the articles by C. Lennhoff, Einar Hollström, and Rudolph Scrimenti bring the history alive by showing how critical their research was to the discovery of EM disease in the U.S. by Scrimenti and even of *Borrelia burgdorferi*, the causative agent of Lyme disease, by Burgdorfer.

In 1920, James Strandberg wrote about the disease and that it was known to be caused by *Ixodes* ticks. Then, Lennhoff, a Jewish researcher and refugee (who fled the war from Norway to Sweden), published research techniques he developed and used to find spirochetes in skin diseases in 1948. While some of those were eventually discounted as "artifact," history may eventually prove him right. Sven Hellerström and Hollström demonstrated an extraordinary example of the compassionate side of science by literally taking Lennhoff into their lab and lives.

In his 1951 paper, Einar Hollström describes EM Afzelius (with the discoverer's name as part of the disease name) as a tick-borne infection that includes central and peripheral nervous system involvement—a fact published first by Hellerström in 1930. He credits Lennhoff's discovery of spirochetes as the reason he was the first to try treating patients with penicillin. However, he noted that patients could relapse or continue with infection if the dose is too

low or if the medication is spread out too far apart.

In 1958, he published an insightful paper characterizing experiences with 77 patients seen over a 9-year period. Treatment studies showed that 3 weeks of penicillin cured about 97% of the patients, with the remaining relapsing and requiring retreatment. He presented a patient who was reinfected after successful treatment, which indicated to him that patients did not develop immunity. His epidemiologic data stated that more women than men get the condition, that people between ages 36 to 60 were more likely to be afflicted, and that cases diminished in the years of dry weather, probably due to fewer ticks in the area. Twenty-seven percent of patients had a known tick-bite.

In 1970, Rudolph Scrimenti wrote about his 1969 discovery of the first U.S. acquired case in Wisconsin. He cites the vector as a tick, the pathogen being a spirochete or rickettsia, and the cure being antibiotics. His patient received rapid, proper treatment of intramuscular penicillin. On follow-up examinations through the years, the patient returned to a healthy active life. Scrimenti was personally encouraged by Hellerström to publish the case that is reprinted in this issue.

How did Scrimenti learn about a disease that rarely affects anyone in the U.S.? His 1993 article gives us the answer to this and the even larger question—how did Burgdorfer know that he was seeing the pathogen of Lyme disease, and not artifact when he looked at the spirochetes in the microscope? As a medical student in 1958, Scrimenti read the paper Hellerström presented at a 1949 Ohio scientific conference. Dr. Burgdorfer, a European scholar, also read the Hellerström paper. It cited *Ixodes* ticks as the vector and Lennhoff's spirochetes as the potential cause of EM disease.

This brings us full circle. Making the old adage "everything old is new again." We will try to bring you Hellerström's historic paper in a future issue, and hope you will cite these works in your future papers.

Spirochaetes in Aetiologically Obscure Diseases

C. Lennhoff

The investigations, on which I am going to report, date in parts as far back as 20-25 years. I was obliged to abandon my notes pertaining to this work when fleeing from Norway, and they must be considered lost. Thus I must ask you to be indulgent if I cannot make definite statements on some points, and it is with particular regret that I find myself unable to give a detailed account of the experiments performed on animals without access to the experimental records. The fact that Prof. Hellerström succeeded in arranging for microscopical specimens of stained spirochaetes previously prepared in Magdeburg to be forwarded from Oslo during the war was of supreme importance for the continuation of the work here in Stockholm.

In 1914 I had published, in *Zeitschrift für Chemotherapie*, a paper dealing with a method of demonstrating *Tr. pallidum* by means of arsphenamine. For this visualization of spirochaetes I made use of the powerful reducing property of the arsphenamine. As reduction indicator I used a mixture of potassium ferricyanide and ferric chloride, from which Berlin blue develops on reduction, as well as silver nitrate solution. Even then I pointed out that especially clear-cut pictures of the spirochaetes are obtained when an ammoniacal solution—suspension of silver nitrate is substituted for the aqueous solution. After immersing a smear containing *Tr. pallidum* first in an arsphenamine solution and afterwards in a reduction indicator of this type the organisms are visualized. Subsequently these findings have been confirmed and amplified by other research-workers. If arsphenamine is injected intravenously into a syphilitic rabbit and the serum taken from the chancre at short intervals is smeared on glass slides, which are treated with the above-mentioned mixture of potassium ferricyanide and ferric chloride, the spirochaetes will be found stained, and progressive morphological changes will be noted

during their gradual disappearance. In my opinion, the immediate action of the arsphenamine upon spirochaetes was established for the first time by this experiment [see Tables 1-10*].

Furthermore, it was found that the spirochaetes of relapsing fever and anthrax bacilli can be stained with arsphenamine; the latter is a specific remedy for each disease. Simultaneously I reported that by using quinine microscopical demonstration is possible of malarial plasmodia by means of the thalleoquin reaction. In this connection it should be mentioned that in 1926, at the *Mittledeutscher Dermatologen-Kongress* in Magdeburg, I was able to show in co-operation with Dr. Kagelmann that the fungi of sporotrichosis can be made visible with iodine. In addition *Tr. pallidum* was made visible by using iodine with gold.

Initially in co-operation with Dr. Kagelmann, I devised a procedure for staining smears containing *Tr. pallidum* with mercury and bismuth. With arsphenamine and bismuth, but not with mercury, microscopical demonstrations successful if the films covering the slides are delicate. When working with bismuth we used Nadisan and Neonadisan respectively, the bismuth absorbed by the spirochaetes being demonstrated by Legère's test or with ammonium sulphide. As regards mercury, a demonstration of the organisms in smears is successful only when working with thick-drop preparations, and in this case a colloidal layer of a certain thickness seems to be imperative. It is also necessary to use a dissociated mercury salt. At present I employ exclusively a 1 per cent aqueous solution of mercuric chloride. Further, it is important to maintain a temperature optimum of between 50°-60°C. For this purpose, we used principally a paraffin thermostat in Magdeburg; here we used a water bath. At low temperatures the action of the mercury salt solution requires a considerably longer time; if the temperature optimum is exceeded, the stain becomes gradually weaker—identification being rendered impossible as far as I can recollect, at 92° C or 96°C. We made a special point of using a well saturated solution of ammonium sulphide.

Briefly, the procedure for staining spirochaetes in thick drops on glass slides is as follows:

Demonstration of spirochaetes in thick-drop and klatsch preparations.

I) Dry in air.

II) Immerse for 10 minutes at 56° C in 1 per cent mer-

Reprinted with permission from Acta Derm Venereol, 1948;28:295-324.

At the time this article was initially published, Dr. Lennhoff was at the Karolinska Institutets Dermatologiska Klinik, Karolinska Sjukhuset, Stockholm, Sweden.

**Note: In the following Tables 1-10, when it is not stated that the pictures were taken from frozen sections, material embedded in paraffin had been used.*

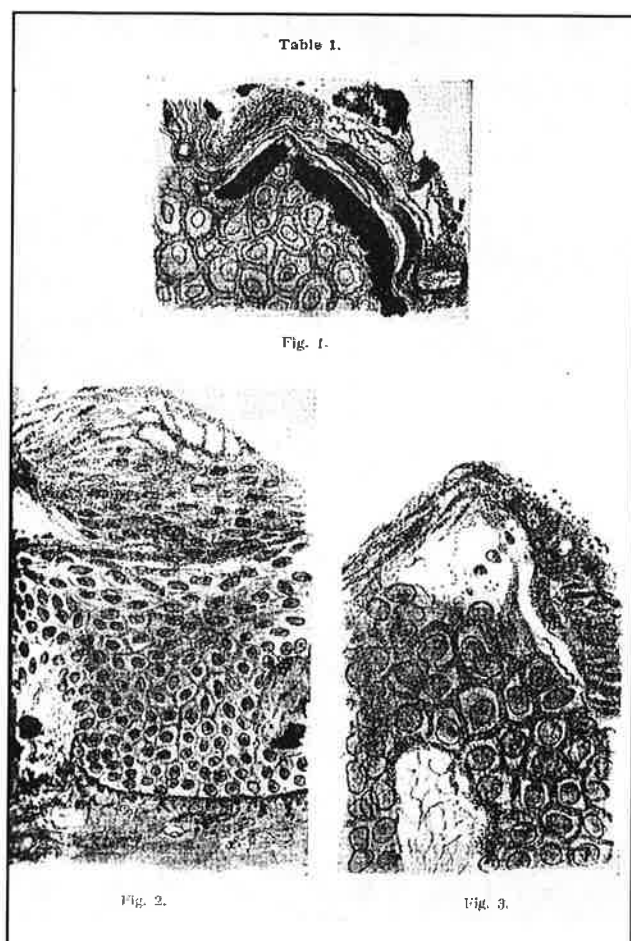


Table 1. (Figure 1) Psoriasis: Spirochaetes in a horny scale; (Figure 2) Psoriasis: Spirochaete between parakeratosis and epithelium; (Figure 3) Psoriasis: Spirochaete beneath the stratum corneum. (Drawing by Professor Felix Pinkus, comp. oc.4. Apochrom. imm. zmm. Figures 4-23 are photo micrographs.)

curic chloride.

III) Pour off the fluid (do not rinse).

IV) Dry with filter paper.

V) Immerse for 20 minutes in well saturated solution of ammonium sulphide (preferably with the slide standing upright in a cuvette).

VI) Pour off fluid.

VII) Rinse. Dry.

Optimal visualization will be obtained by following the above directions. If, however, it is only a matter of a practical demonstration of the spirochaetes, the periods of time specified, especially that of the ammonium sulphide treatment, may be considerably abbreviated. On the other hand, the specimens may quite well be exposed for several hours without injury at 56° C to the action of the mercuric chloride solution.

From the time spent in Magdeburg I still possess specimens, in which spirochaetes were demonstrated in thick drops of material taken from cases of tertiary syphilis. However, it was first here in Stockholm I recognized that this method of demonstrating *Tr. pallidum* is quantitatively superior to the dark-field technique, though of course it is no substitute for observing the organisms in motion. Here we met with 12 instances of primary lesions, in which no spirochaetes could be found on dark-field examination, whereas their presence was disclosed by the above procedure. In these cases we proceeded by first taking serum for dark-field examination, then for the thick-drop stain, and finally again for dark-field examination. These latter examinations were carried out by at least 2, in a few instances even 3, different investigators, the result each time being negative. In spite of these negative findings, spirochaetes were observed in the thick-drop preparations, sometimes even in large numbers. In a case of secondary syphilis the result was identical. Out of 3 instances of lymph node aspiration on darkfield examination no spirochaetes were detected in 2 cases and a single spirochaete in 1 case, while on the other hand in the thick drop organisms were easily demonstrated, sometimes in large numbers.¹

Moreover, my researchers here in Stockholm on this thick-drop procedure yielded results that were quite useful in yet another way. As you will hear presently, I was able to establish the presence of elements resembling spirochaetes in appearance in quite a considerable number of aetiologically obscure conditions. These spirochaetes are susceptible to staining if a glass slide is lightly touched with the dermal surface of an excised piece of skin, or another tissue specimen, *visa versa* (klatsch technique). In this manipulation pressure should be avoided, otherwise numerous fibrils and filaments are apt to be stained as well, which would render recognition of the spirochaetes difficult or, in occasional instances, actually impossible. The best results are obtained, e.g. in lichen ruber, if after contact with the specimen a droplet of tissue fluid remains on the slide. Naturally this klatsch procedure is not so conclusive for determining the pathogenicity of a given spirochaete as one that discloses the position of the organisms within the tissues. The technique, however, is simple and does not require much time. For demonstrating *Tr. pallidum* at an autopsy the method seems to be definitely useful.

Before proceeding to discuss the experiments performed on animals with bismuth and mercury. I should

¹Addendum to proofs. Since reading this paper before the meeting, I have examined material obtained by lymph node aspiration in cases of varying skin diseases. These findings will later be reported elsewhere.

Table 2.

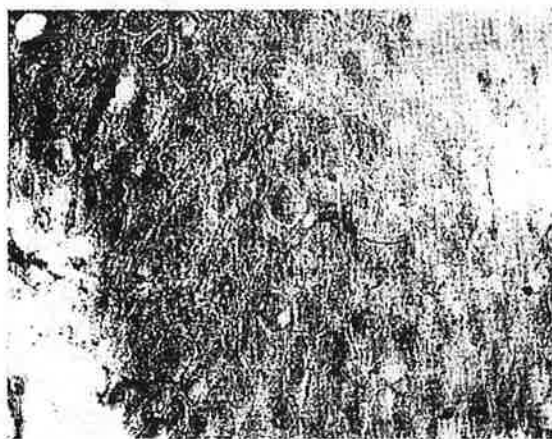


Fig. 4.

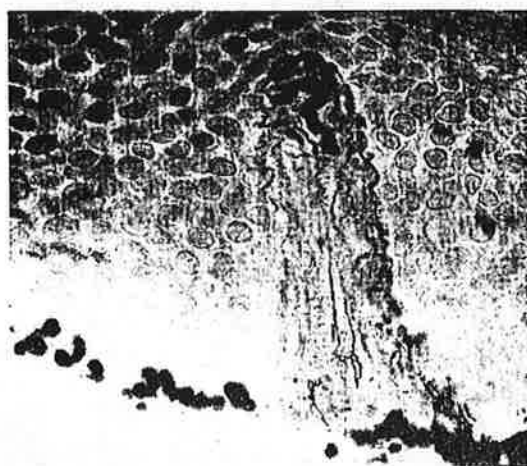


Fig. 5.

Table 2. (Figure 4) Psoriasis: Spirochaete in the epithelium. Frozen section. X600; (Figure 5) Psoriasis: Spirochaete in a papilla. X 600.

like to mention a preliminary investigation. If a rabbit is injected first subcutaneously with mercuric chloride solution, and immediately afterwards intravenously with a solution of sodium thiosulphate, a dark, smoky discoloration will presently appear at the site of the sublimate injection, due to the presence of an active sulphur compound, such as e.g. sulphuretted hydrogen, into which compound the sodium thiosulphate is rapidly turned even in the alkaline system. Many years after this experiment, during my stay in Oslo, I learned from a paper by Oppenheim that as early as in 1896 the pharmacologist Faust of Vienna had by another method of approach arrived at the result that sodium thiosulphate is instantaneously transformed within the system. When he injected

a lethal dose of potassium cyanide together with sodium thiosulphate into mice, the animals survived. If a syphilitic rabbit presenting a chancre teeming with spirochaetes is given an intravenous injection of sodium thiosulphate the organisms will on dark-field examination have disappeared immediately, i.e. after the minimum time required for preparing the specimens. After some time spirochaetes may again be seen, thus showing—and this I ask you to bear in mind for the following discussion—that sulphur is an antisymphilitic, as had formerly been pointed out by other investigators as well; its curative action upon syphilis is, however, not a lasting one. i.e. if any conclusion at all may be drawn from the above experiment. If a syphilitic rabbit is injected intravenously with Nadisan or Neonadisan and subsequently with sodium thiosulphate, and then serum is taken from the chancre at short intervals, spirochaetes that are stained black will be found, the black stain being due to bisulfide having been absorbed by the organisms in the system of the rabbit. If my memory does not fail me, we have carried out corresponding experiments with Neonadisan and sodium iodate administered intravenously. Experiments with mercury, which could only be carried out on rabbits, proved difficult. Obviously, there are certain differences between, on the one hand, the action of arsphenamine and bismuth and, on the other, that of mercury. I am, however, not able to give details.

If Salyrgan, a colloidal mercury preparation, is injected into the chancre of a rabbit and immediately followed by an injection of sodium thiosulphate into a vein, spirochaetes stained black will be found in the serum subsequently taken from the chancre. If my memory does not deceive me, it was recorded that we found spirochaetes showing the black stain as early as 2 minutes after the sodium thiosulphate injection. If a syphilitic rabbit is injected intravenously with Salyrgan and sodium iodide, then I seem to recall that the spirochaetes can be seen stained red, i.e. by mercuric iodide. Unfortunately, I am unable to give details of these experiments carried out so long ago, as pointed out in the introduction to the present paper.

The possibility of demonstrating spirochaetes with mercury has hitherto attained the greatest importance. With the assistance of Miss Koehne in Magdeburg, I had evolved a mercury impregnation method for spirochaetes situated in the tissues. Though as yet not free from considerable imperfections, it still seems capable of demonstrating not only the spirochaetes susceptible to the silver stains, such as *Tr. pallidum*, but in addition other spirochaetes hitherto unknown.

Before considering this method I will try to give you an idea of the reasoning that led me to it. The starting-point of my investigations constituted my endeavors to

Table 3.

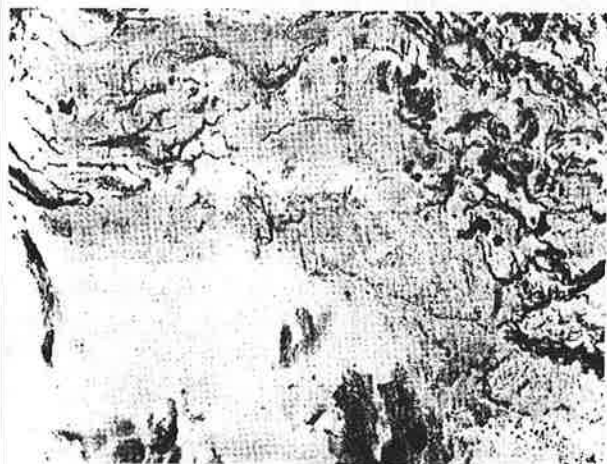


Fig. 6.

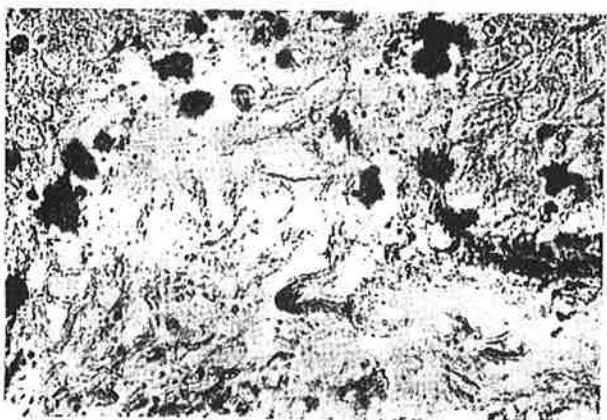


Fig. 7.

Table 3. (Figure 6) Psoriasis: Spirochaetes in the dermis. X 600; (Figure 7) Psoriasis: Spirochaete in a papilla (case from which the oldest culture was obtained) X 600.

find an avenue of approach to the pathogenesis of psoriasis. Round about 1912, in Bern, I had demonstrated to Jadassohn and some of my fellow-assistants some Giemsa-stained spirochaetes in a klatsch preparation made from a psoriasis cuticle. This occurred, as we later found out, about the same time a Prowazek, and also Peller, of Nobl's clinic published their findings. Subsequently, during the first World War, I had carried out inoculation experiments on psoriasis patients, a report of which was published in *Berliner Klinische Wochenschrift* in 1920. Afterwards these inoculation experiments were continued and extended by Dr. Kagelmann in Magdeburg; the results have not been published. In 1920, Rask reported to have found spirochaetes

in psoriasis, which was universally rejected. However, although most of his observations fail to withstand criticism, a picture showing spirochaete-like elements within the epithelium is truly remarkable. In 1940, when staying in Oslo I called in person on Dr. Rask and told him that, if he could describe his method so that other workers would be able to repeat his demonstration of spirochaetes in the tissues, he would, in my opinion, have been the first to contribute material evidence of the pathogenetic significance of spirochaetes in psoriasis. Dr. Rask was unable, however, to make any statements as to his technique in addition to what he had published.

In 1921, at the *Mitteldeutscher Dermatologen-Kongress* in Halle, I had demonstrated a crystal violet stain which, owing to a misapprehension of my manuscript, was stated by Hoffmann and Hoffmann in Jadassohn's handbook to be unstable. Using this stain I also had found elements resembling spirochaetes in smears prepared from a psoriasis cuticle. However, since fibrin was also made visible with this method and since, in addition, it failed to yield information as to the position of the elements observed within the tissues, I regarded these findings as of minor importance. Yet when in Oslo, 1940, I found again among my papers the sketches made from my preparations by Dr. Kagelmann in 1920 or 1921, I felt that I had before me spirochaetes identical with those I had later demonstrated in the tissues. A series of examination of psoriasis lesions for spirochaetes carried out with the conventional silver stains failed to give any particularly significant results.

Especially encouraging to me in my endeavors was the observation that a considerable proportion of psoriasis cases heal under treatment with mercurous iodide (the *Hydrargyrosus jodidum* of the Swedish Pharmacopoeia). This fact I had mentioned briefly in a discussion at the *Leipziger Naturforschertag* in 1922. To quote the expression I used on that occasion. "the trees will not grow sky high." that is to say, only in a proportion of the cases is a cure brought about, and relapses occur as with all the other methods; on the other hand, the number of cases cured by mercurous iodide exceeds that of the responses to arsenic. This therapeutical experience was supplemented by the discovery of the corymbose psoriasis, presented by myself at a meeting of the Magdeburg Medical Society, and reported by Kagelmann in *Archiv für Dermatologic*, vol. 146. These observations constituted a very strong incitement to attempt a demonstration of spirochaetes by means of mercury, in view of the parallelism between therapeutical action and microscopical visualization. Since I in co-operation with Dr. Kagelmann succeeded in demonstrating *Tr. pallidum* with the thick-drop procedure, it seemed desirable to evolve a method of visualization in the tissues which was

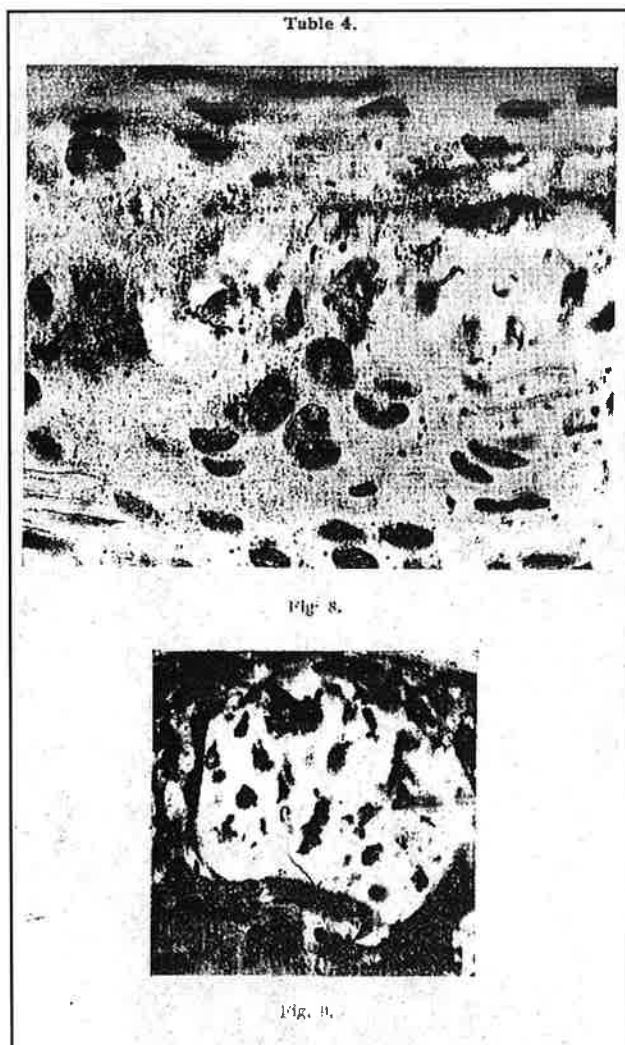


Table 4. (Figure 8) Psoriasis: *Spirochaete* in a micro-abscess. X 1,000; (Figure 9) Pustular psoriasis: *Spirochaete* in pustule. X 600.

done with the assistance of Miss Koeine.

As with silver staining, thin tissue specimens are immersed in concentrated solutions of mercuric chloride in absolute alcohol. Here in Stockholm we prolonged the alcohol treatment as compared with our previous procedure, the specimens now being kept for 6-9 months in this concentrated alcoholic mercuric chloride solution. Naturally, great care must be exercised in preventing solution from evaporating during this long period. For this purpose the flasks are closed with well-fitting, paraffined corks and periodically examined for the formation of precipitates. Subsequent to the mercuric chloride treatment the specimens are rinsed in running water for 15-21 hours and afterwards immersed for 6-9 hours in an aqueous solution of ammonium sulphide. Here also the flasks must be tightly closed. Prior to being used with tissue

specimens, each fresh batch of the ammonium sulphide is tested as to its efficacy with think-drop preparations of syphilitic chancre serum on glass slides. The reagent is then sorted under paraffin in a refrigerator. It will now retain its applicability for at least a month. If stored for longer periods, the ammonium sulphide will deteriorate and assume a brownish tinge. The reagent must possess a satisfactory quality to ensure the success of the visualization. In Magenburg the drug was ordered from a firm of chemical manufacturers, here it has been supplied to us of late by the Chemical Department of Karolinska Institutet. In order to ensure complete saturation of the ammonium sulphide solution, hydrogen sulphide is bubbled through an ammoniacal solution for 8-9 hours. After having been treated with ammonium sulphide the specimens are immediately immersed in absolute alcohol, which as a rule is twice changed, and as quickly as possible transferred into paraffin via xylene. If the specimens have been left in the mercuric chloride solution for too short a time, the mercury with which the spirochaetes are impregnated may be dissolved by the ammonium sulphide or the stain may be destroyed during the process of embedding. In this connection I wish especially to point out a technical error I occasionally made here in Stockholm. As already emphasized, very thin slices of tissue should be taken for examination. At the out-patient department I had removed pieces of skin by shallow excision with a scalpel, subsequently spreading these upon a covering glass or a piece of filter-paper in order to prevent the margins from doubling up. Even if the specimens are separated from these supports after the lapse of only a few minutes, the staining of the spirochaetes in the dermin will be found to be less satisfactory, if not completely destroyed, within the areas that were in contact with the support. The specimens should therefore be transferred into the alcoholic mercuric chloride solution without employing a support of this type. By using a 5% aqueous mercuric chloride solution instead of concentrated alcoholic mercuric chloride solution the period of treatment can be extended up to 3-6 months. With this modification, however, fibrils and filaments are apt to stain too, thus obstructing examination. Even the alcohol method fails to afford complete protection against the coincidental staining of fibrils. This applies particularly to specimens of facial skin undergoing senile degeneration, and was especially noted when examining lesions of erythematouides. The 5% aqueous solution has proved very useful in demonstrating spirochaetes in cases of eryptive fevers, particularly rubella, which had initially given rise to considerable difficulties. However, when a biopsy specimen, taken from a rubella patient on the first day of the eruption, was kept for 6 months in concentrated alcoholic mercuric solution, i.e. longer than at the start

Table 5.



Fig. 10.



Fig. 11.



Fig. 12.

Table 5. (Figure 10) Pustular psoriasis: *Spirochaete*, and perhaps *spirochaetal* debris, in a pustule. X 600; (Figure 11) Pustular psoriasis: *Spirochaetes* in a pustule. X 600; (Figure 12) Same area as in Fig. 11. X 1,000.

of the investigations, the presence of spirochaetes was disclosed by this solution also. Attempts to accelerate considerably the action of the mercuric chloride solution by employing higher temperatures about 50C., have resulted in fairly satisfactory and sometimes excellent, visualization of the spirochaetes in a number of cases without producing consistently reliable results. I will however, refrain from discussing these experiments. Even our alcoholic mercuric chloride procedure still needs improvement. A serious drawback with regard to skin is that the spirochaetes situated within the epithelium are stained only in the marginal zones or in those areas where the epithelium is partly broken up by the morbid process. In some cases we have therefore scarified the epithelium with the scalpel; in Magdeburg—this modification was not used by us in Stockholm—we had also achieved visualization in the epithelium by omitting to embed the specimens. Instead, these were dipped for a moment in distilled water subsequent to the mercuric chloride treatment. Frozen sections were then made

which were stained on the slide with ammonium sulphide. In this procedure the section should be carefully dried on the slides with filter-paper, as they otherwise are apt to fold up when the ammonium sulphide solution is applied. This procedure sometimes met with certain technical difficulties; in such cases it was modified as follows: The wet frozen section is placed upon a slide which is laid, with the section facing downwards, on a cuvette-cover containing ammonium sulphide. Care is taken that the cuvette cover is well closed by the slide. The period during which the solution, or vapours, of ammonium sulphide are allowed to act on the specimen, is 3-20 minutes. Briefly summarized, our tissue procedure principally used at present is the following:

Demonstration of spirochaetes in tissue specimens.

I) Immerse the thinnest possible tissue pieces for about 6-9 months in:

Mercuric chloride 25.0,

Absolute alcohol 75.0 (closed flask with paraffined cork).

II) Rinse for about 15-21 hours in ammonium sulphide.

III) Immerse for about 9 hours in ammonium sulphide.

IV) After rapid transfer via alcohol and xylene, embed in paraffin. Frequently we employ counterstaining with haematoxylin and van Gieson's solution.

In addition to the examination of tissue specimens in Magdeburg we attempted to demonstrate the spirochaetes of psoriasis, seborrhoeic eczema; lichen ruber and pityriasis rosca with the aid of the dark-field procedure. As it is not possible in these diseases to obtain serum for dark-field examination in the same way as in syphilis, we evolved the following technique.

When dealing with psoriasis, seborrhoeic eczema and pityriasis rosea, we collected a liberal amount of scales or, as was most often done in case of lichen ruber, tissue material. The material obtained was ground in a sterile mortar, suspended in saline and—in order to remove coarser particles of tissue—strained through a single or double layer of sterile fine linen, occasionally also through a Seitz filter. The filtrate was centrifuged for 20-45 minutes at 3,000 revs/min, and the supernant fluid then drained off by means of a water-jet pump, with the exception of a minute amount covering the bottom of the tube and kept for dark-field examination. As regards psoriasis, I remember the figures quoted in the records: the number of spirochaetes found in a given case was small in spite of the lengthy mostly 6-7, in exceptional instances only 2 and at the utmost 30. The organisms were coarse and moved in a characteristic, transversely wabbling fashion. According to the records, we have found spirochaetes in 94 of 96 psoriasis cases with the procedure described.

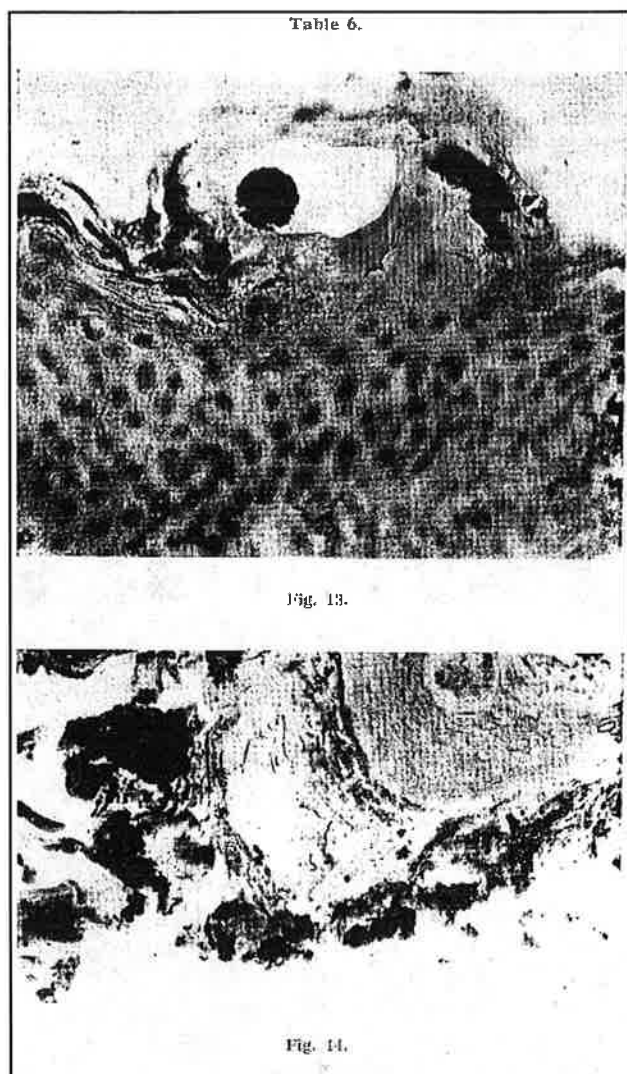


Table 6. (Figure 13) Psoriasis: Spirochaete in a vesicle wall. The black mass within the vesicle is precipitated mercuric sulphide; (Figure 14) Seborrhoic eczema: Spirochaetes adjacent to a hair follicle. X 600.

I am unable to recall the actual figures for seborrhoic eczema, lichen ruber and pityriasis rosea. As far I know, we examined about 15 cases each of these diseases with darkfield technique, with positive findings in 12-14 cases of each disorder. In these examinations we were unable to distinguish between the spirochaete of seborrhoic eczema and that of psoriasis. In accordance with its appearance in stained sections, the spirochaete of lichen ruber is delicate, and moves gracefully, i.e. without displaying the so-called "twisting" motion of *Tr. pallidum*. The spirochaete of pityriasis rosea moves with extraordinary velocity, often tumbling head over heels in its motion, and is in this state not recognizable as a spirochaete; when the organism has resumed its horizon-

tal position however, its true character of a spirochaete will be revealed.

Hitherto we have not been able to take up work with the tedious procedure of dark-field examination as no centrifuge has been available. However, we have carried out a few preliminary experiments using simplified technique by scraping a small amount of tissue material from the dermal surface of the excised specimen into a drop of saline. Thus we were able to find spirochaetes, which in various instances were demonstrated to several gentlemen, in 13 cases of psoriasis, 5 of pityriasis rosea, 1 of seborrhoic eczema, 2 of lichen ruber, 3 of erythema exsudativum multiforme, and 1 of erythema nodosum.

Further, in Magdeburg, we had succeeded in growing the spirochaetes of psoriasis, lichen ruber and pityriasis rosea on culture media. The organisms were grown in a refrigerator at 5-8°C on two media introduced by Reiter and Hoder respectively; growth was arrested at 37°C.; the optimal temperature was not ascertained. However, when dealing with other spirochaetes, the temperature most conducive to growth should generally be considered of interest, as this might prove capable of explaining the presence of particularly large numbers of spirochaetes in the skin, and of illuminating certain clinical aspects, e.g. in cases of eruptive fevers. When I was compelled to resign my appointment, the oldest psoriasis strain was at the 28th subculture. The transfers had been made at fortnight intervals, the purity of the strain having been controlled in the 8th or 9th subculture. Cultivation had been carried out by Miss Rilke. Recently we resumed cultivation in a refrigerator in co-operation with Docent Hollström; hitherto we have obtained first cultures grown in Hoder's medium from cases of psoriasis and pityriasis rosea, also from those of erythematodes and erythema multiforme, the organisms of which have not been grown previously. In these experiments we used a medium prepared with rabbit-serum broth and rabbit liver thrice subjected to fractional sterilization (Hoder, Z. Immun. Forsch. 1930).

Hitherto, I have mostly been concerned with demonstrating spirochaetes in tissue specimens, but I must refrain from discussing details. However, I wish to stress the fact that careful attention was paid as to whether or not the elements interpreted by us as spirochaetes were situated *in loco morbid*. Below, the term spirochaete will be used to design elements presenting the morphological aspect of spirochaetes, whether the living organisms have been studied in the dark-field or not. Firstly, I propose to give a tabulation of the diseases in the question:

Psoriasis, seborrhoic eczema, lichen ruber, pityriasis

¹Addendum to proofs: In addition, granuloma anulare and bromoderma(?).

Table 7.

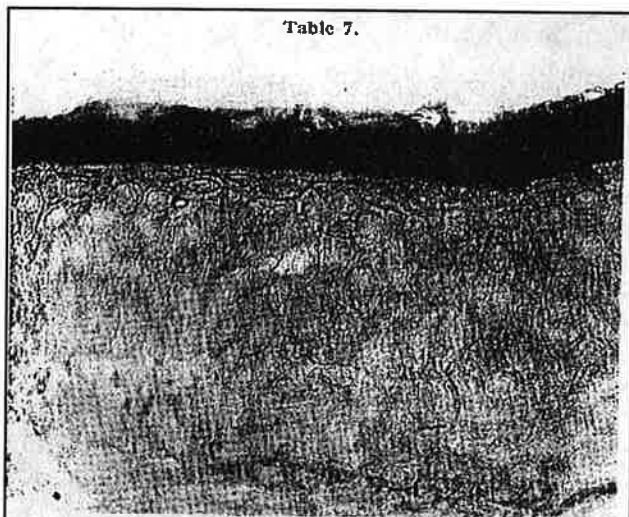


Fig. 15.

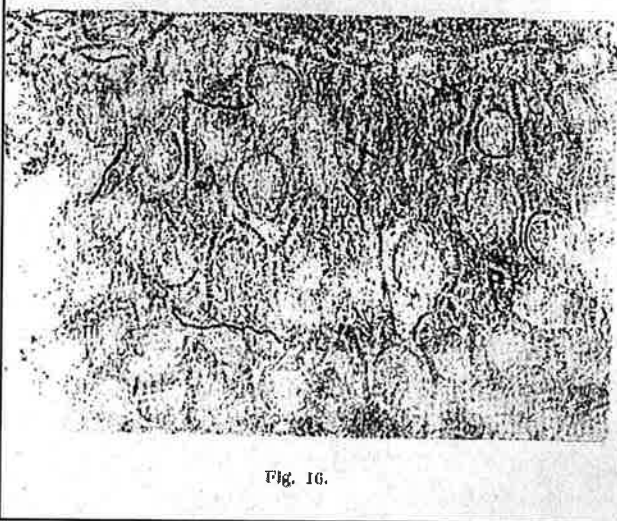


Fig. 16.

Table 7. (Figure 15) Lichen ruber: Spirochaete in the epithelium. Frozen section. X 600; (Figure 16) Same area as in Fig. 15 X 1,000.

rosea, erythematodes, erythema multiforme, erythema nodosum, zoster, varicella, morbilli, rebella, dermatitis herpetiformis, permphigus, mycosis fungoides, parapsoriasis, lymphadenosis cutis benigna, lymphogranuloma inguinale, lymphogranulomatosis maligna, lymphogranulomatosis benigna, erythema migrans, acne necroticans, acne vulgaris, endocarditis and leucaemia.¹

We have examined about 210 cases of psoriasis in all. In Magdeburg, on examination of skin sections, 72 out of 80 cases were positive, in Stockholm all the 52 examined cases were positive. This also applies to material obtained from Koebners phenomena. In addition, there

were in Magdeburg 96 cases with dark-field examination, 92 of which were positive; in Stockholm we obtained 13 positive dark-field findings. When stained in the tissues, the spirochaete is as a rule rather coarse, with occasional delicate specimens. Therapeutically, psoriasis responds to spirochaetocides, arsenic and mercurous iodide, as I have mentioned earlier; furthermore gold, bismuth and iodine have been recommended for treatment. Following the administration of arsphenamine and gold psoriasis-form eruptions have been observed.

Of seborrhoeic eczema altogether 27 cases were examined. Therapeutically, in addition to ammoniated mercury ointment sulphur is used principally; the latter is a spirochaetocide.

In lichen ruber another delicate spirochaete is present, which is distinguishable from that of psoriasis not only on dark-field examination but also in sections. In spirochaete observed in cases of lichen ruber the coils are generally somewhat wider and more shallow than in *Tr. pallidum*. The characteristic spirochaete was demonstrated in about 60 cases in all, among which there was one showing occasional organisms in a Koebners phenomenon, and one organism was found in a lymph gland forwarded for examination by Docent Hollström. In addition, there were 2 further cases which, in my opinion, are of general significance. In each of 2 eruptions resembling lichen ruber, which had developed subsequent to the administration of arsphenamine and mercury respectively, I found spirochaetes identical with those otherwise observed in case of lichen ruber. In addition to the lichen ruber caused by the use of arsphenamine and mercury, lichen ruber is also known to develop especially after chrysotherapy, as gold is also a spirochaetocide. Lichen ruber may be cured by arsenic, mercurous iodide and bismuth, i.e. by spirochaetocides, but may also be provoked by spirochaetocides. As is well-known, considerable credit is due to Milian for having pointed out, in general terms, the significance of the provocation of a latent microbism. Apparently this factor plays an especially important role in the field of dermatology, as regards the spirochaetocide that simultaneously exert a curative action on the condition concerned.

The total of pityriasis rosea cases examined amounts to about 80, practically all of them being positive. As a rule, the spirochaete is delicate in shape with narrow coils, both shape and size, however, being subject to considerable variations: there exist also fairly large and coarser forms, and organisms with quite shallow coils as well as such forming arcs and circles are comparatively frequent. Previously it had been contended by Saalfeled that pityriasis rosea is cured by arsenic; here it was established that a prompt cure results from bismuth and arsphenamine. A report on this observation will be give

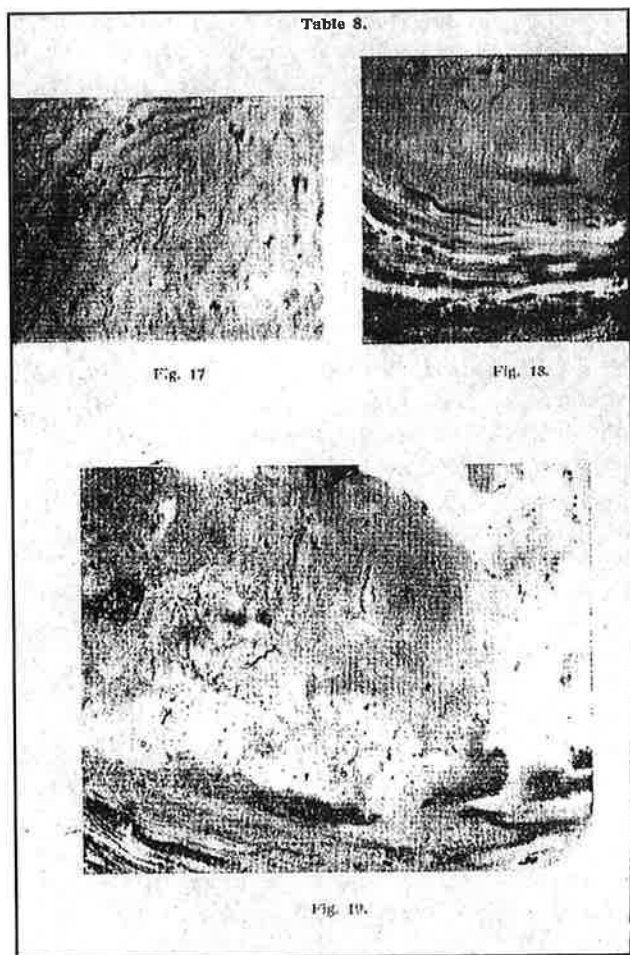


Table 8. (Figure 17) Lichen ruber: Spirochaete in an infiltrate. X 600; (Figure 18) Lichen ruber bullosus: Spirochaete in a vesicle. X 600; (Figure 19) Same area as in Fig. 18 X 1,000.

by Docent Hollström, the first to have treated pityriasis rosea with bismuth. Evidence is on record of pityriasis rosea being provoked by gold and arsphenamine.

Of erythematodes we have examined 60 cases in all, consistently with positive spirochaetal findings. In addition there are 3 cases of which cubital lymph glands were forwarded for examination by Dr. Thyresson. The lesions clear up after administration of gold, arsphenamine, bismuth and also mercurous iodide, as has been established by us here in Stockholm in experiments extending over a considerable period. According to Martensrein and Granzow the luetin reaction is positive in 75 per cent of the cases i.e. as frequently as in tertiary syphilis. The Wassermann test is not infrequently positive in the acute cases, being positive in chronic cases if the amount of antigen is doubled. The relation between erythematodes and tuberculosis or streptococcal infection might possibly be interpreted on the basis of provocation of a latent

microbism, which also applies to erythema nodosum. Again, the occurrence of tuberculosis subsequent to morbilli has been known for a long time. Parentetically, I should like to mention that once in a case of erythematodes presenting symptoms of arthritis, I found spirochaetes in an endocarditic heart valve; I am unable to state whether in this case the endocarditis was due to the erythematodes, or was merely a case of (so called rheumatic endocarditis). Furthermore, I once demonstrated spirochaetes in a valve in a case of rheumatic endocarditis, and twice in lymph glands of patients suffering from rheumatic polyarthritis. I am not aware, nor have I investigated, whether salicylic acid acts as a spirochaetocide.

I have examined 27 cases of erythema multiforme in addition to one case examined in Magdeburg. Among these, the findings were negative in sections in one case, doubtfully positive in another case, and positive in the remainder. One case of erythema multiforme with sparse nodular lesions following on the administration of sulfathiazole was positive. Besides salicylic acid, potassium iodide is recommended for treatment and, in relapsing cases, arsenic; possibly also prevention occurs brought about by salicylic acid arsenicals and mercury.

8 cases of erythema nodosum have been examined (tissue specimens), with positive findings, and I demonstrated the organisms in the dark-field in once case to several colleagues. In addition, there were 7 cases of erythema nodosum after the administration of sulfathiazole which were positive. As is well-known, Massinsi reported a long time ago that on darkfield examination in a case of erythema nodosum he had found spirochaetes which he was unable to stain whichever method he employed.

I have examined 34 cases of zoster, yielding positive results by me. Provocation has been described as being due to arsenic and its derivatives, potassium iodide, bismuth, mercury and Chrysoglan. Varicella infection from arsenic zoster has both been observed and experimentally produced. Provided the virus is the same in both diseases, the transfer, of the arsenic zoster and its manifestation in the form of varicella may be considered to support the conception of the provocation of a latent microbism.

I have examined 15 varicella and 7 morbilli cases. In a case, in which Docent Hollström consulted me on the first morning of the morbilli eruption, I found 4 spirochaetes with peculiar, twisting movements in the blood after a dark-field search of about 15 minutes. Salimbeni and Kermorgani, of the Institute of Pasteur, stated that they were able to culture at 32°C spirochaetes from morbilli blood collected prior to the development of the rash; they failed, however, to obtain a pure culture. As regards provocation, Milian has reported a case of morbilli after arsphenamine entailing infection of other

Table 9.

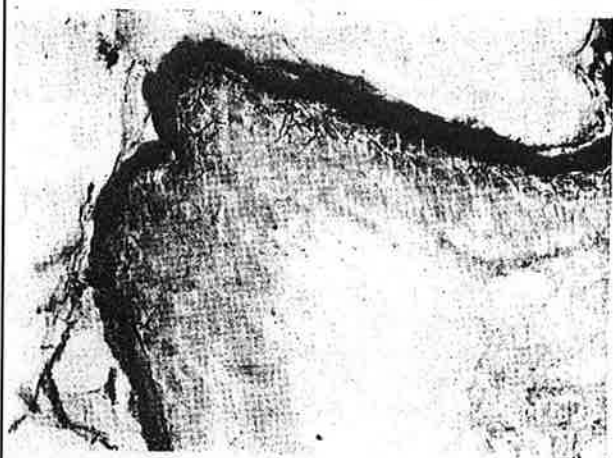


Fig. 20.

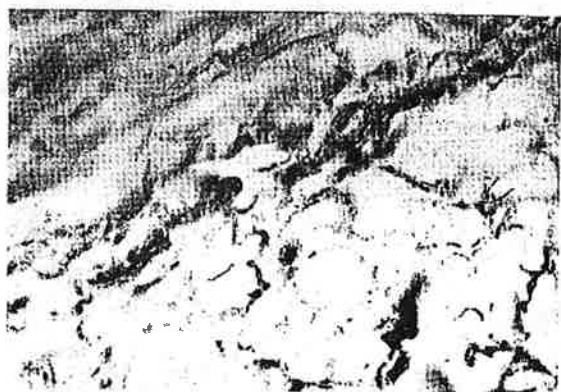


Fig. 21.

Table 9. (Figure 20) Pityriasis rosea: Spirochaete in the epithelium. Frozen section. X 600; (Figure 21) Pityriasis rosea: Spirochaetes in the dermis. X 1,000.

persons.

I have examined altogether 13 cases of rubella. Prior to being able to examine sections, I had made a klatsch preparation showing definitely peculiar spirochaetes with which I was unfamiliar. I mentioned this at the time when demonstrating the preparation to Professor Hellerström, Docent Ringertz and other gentlemen. This was the first and only instance that I seemed to have identified a new spirochaete solely on the basis of a klatsch preparation. In addition to the findings discussed

¹Addendum to proofs: Subsequently 3 cases of erythema migrans received bismuth treatment, 2 of which with striking success; the third case, which is still under treatment fails to show a rapid improvement.

above, I have met with a case of rubella after sulfathiazole and another one after arsphenamine, each of the positive. In the latter case typical lymphoglandular enlargement was noted in the occipital triangle, I am not aware of benign eruptive fevers having been treated with spirochaetocides. I was not afforded the opportunity examining cases of scarlet fever.

I have examined 7 positive cases of dermatitis herperiformis. Also in this disease I consider provocation by spirochaetocides possible. There are cases in which the condition develops for the first time in previously healthy subjects after the administration of iodine or mercury and takes a course exactly identical with that observed in dermatitis herperiformis, arising without any known excitive factor. As far as I know, there is no evidence of a reaction of supersensitiveness with such a course. Should it emerge on continued investigation that the local responses to iodine and mercury respectively are due to provocation, this observation would be of considerable interest.

I shall not discuss these conditions as I have examined only a few cases. The common feature is the therapeutic use of spirochaetocides. To my knowledge this is at present not known to apply to erythema migrans.¹

I have examined 10 cases, of acne vulgaris but these were not exhaustively investigated; in the first place, the objection can be raised that positive spirochaetal findings might be due to a schorrhoic eczema conducive to the origination of the acne. Of lymphatic leucaemia I have collected 6 cases with positive findings, in one of which a positive klatsch preparation was obtained from bone marrow. Of myeloid leucaemia, there are 2 cases, one of them with a positive klatsch preparation of bone marrow. Therapeutically arsenicals should be taken into consideration. Possibly also the leucaemoid reaction to mercury results from provocation.

Further more, I would like to mention that I have found spirochaetes in closed cancerous tumours; I do not propose, however, to discuss this observation until further thorough investigations have been made.²

In one instance we found spirochaetes in a horny scale covering a soft naevus, and in another in a scale adhering to lipoma, in neither case, however, in the tissues. Spirochaetes were not demonstrated in allergic eczema, Besier's prurigo, lupus vulgaris, a case of glandular tuberculosis, mycotic lesions, a case of Recklinghausen's disease, nor in a case of pseudomyxoma peritonei and one of glomerulonephritis. These constitute some few controls, but naturally the range of control examinations

²Addendum to proofs: Since the time of the Meeting the number of examinations has increased. I refrain, however, from giving data as to these continued investigations in correcting the proofs.

Table 10.

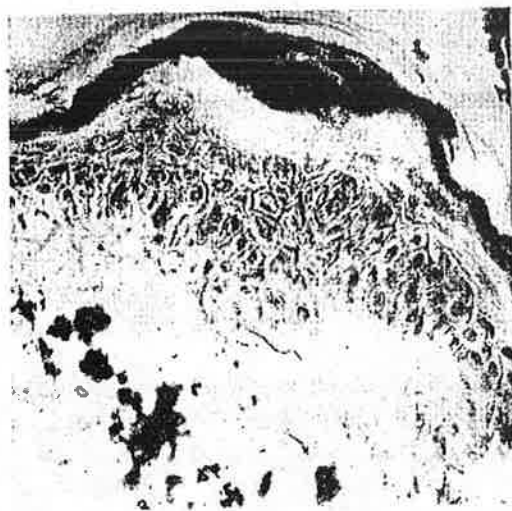


Fig. 22



Fig. 23.

Table 10. (Figure 22) Morbilli: Spirochaete in the dermis. X 600; (Figure 23) Zoster: Spirochaete in the dermis. X 1,000.

must be considerably extended. At the present moment the observations indicate that spirochaetes are not present in all conditions, nor at all stages of their development.

In summarizing, I should like especially to emphasize the following. On the basis of the parallelism between therapeutic action and microscopical visualization, a procedure was evolved whereby, with the aid of mercury. *Tr. pallidum* and new, unknown spirochaetetes could be demonstrated. As to *Tr. pallidum*, the thick-drop procedure seems to be quantitatively superior to the dark-field technique, though naturally incapable of replacing the latter.

The spirochaetes preciously known are susceptible to

the silver stain, that is to say, they are argentum-positive; but it has been occasionally suggested that even this group includes argentum-negative forms (Hollande, Hoffmann and Karrenberg). The new, apparently very numerous spirochaetes are (generally?) argentums-negative. This is probably one of the reasons for their hitherto having escaped observation; another one is perhaps the fact that when dealing with the conditions in question, serum for dark-field examination cannot be obtained by so simple a procedure as that with which we are familiar in the examination of syphilitic lesions.

In the diseases, in which spirochaetes are present, treatment with spirochaetocides and provocation by the same seems to play an important part. Many observations suggest that toxicodermas presenting the aspect of idiopathic diseases are actually identical with the conditions they stimulate.

It is generally known that identification of the spirochaetes depending entirely on morphological characteristics as displayed in the fixed condition is as a rule impossible; however, the spirochaete of psoriasis can be distinguished from that of lichen ruber even in tissue specimens. The new spirochaetes hitherto examined with the dark-field technique are distinctive for various diseases.

In Magdeburg the spirochaetes of psoriasis, lichen ruber and pityriasis rosea have been cultured in a refrigerator. Recently, in co-operation with Docent Hollström first cultures have also been obtained from psoriasis, pityriasis rosea, erythematodes and erythema multiforme. The organisms of both the latter diseases have not previously been grown.

As for the majority of the conditions examined, it is present more or less likely that spirochaetes are of aetiological significance. In my opinion, as regards psoriasis, lichen ruber, pityriasis rosea and erythematodes, the aetiological evidence for these being spirochaetoses is largely established; in the cases of erythema multiforme I consider this highly probable. However, it should be strongly emphasized that as yet only the foundation is laid for further necessary investigations.

I have now come to the end of my thesis but before concluding I wish to express my deeply-felt gratitude to my former associates. In the first place, my sincere thanks are due to Professor Felix Pinkus, who after a long interval of involuntary leisure has given me highly valuable advice and assistance at a preliminary general survey of my precious specimens during our simultaneous stay in Oslo. From that period also dates my gratitude towards Professor Victor Kafka, who has encouraged me to be taking especially keen interest in my work. Here in Sweden, I am first and foremost greatly indebted to Professor Sven Hellerström, who immediately wel-

comed me to his clinic and facilitated my work in every respect, as well as to the Prosectors of the Pathological Institute of St. Göran's Hospital, Dr. Fredrick Wahlgren and Dr. Nils Ringertz, who afforded me the opportunity of working in their institute and continually gave me their support. Furthermore, I proffer my thanks to Physician-in-Chief Docent Bo Tarras-Wahnberg and to all other gentlemen who extended their kind help to me. However, in all probability I would not have been able at all to express my gratitude, had not Sweden received us refugees and afforded us the opportunity of working. To Sweden, therefore, our heartfelt thanks are addressed.

At the 11th meeting of the Northern Dermatological Society, on June 9th, 1946, the following original preparations were demonstrated under the microscope:

- I) *Tr. pallidum*, thick drop preparation.
- II) Spirochaetes in papilla, psoriasis.
- III) " in a vesicle, lichen ruber bullosus.
- IV) " in the dermis, pityriasis rosea.
- V) " in the epithelium, erythematodes.
- VI) " at the lower epithelial margin, erythema multiforme.
- VII) " in a lymph gland, myeloid leucaemia.

Successful Treatment of Erythema Migrans Afzelius

Einar Hollström

An efficacious method of treating erythema chronicum migrans has not been known formerly, nor was it considered strictly necessary to treat that condition as causing but mild discomfort. Since, however, erythema migrans has been shown in a proportion of instances to involve the central and peripheral nervous system (Hellerström, 1930; Bode, 1933; Bing, 1945; Gelbjerg-Hansen, 1945; Sälde, 1946; Dalsgaard-Neilsen and Kierkegaard, 1947; Leczinsky, 1949),¹ at the present moment the question of successful treatment is of current interest even from the practical point of view. On the other hand, the aetiology of the condition being obscure, apart from the established fact that in the major proportion of instances the eruption follows upon a tick bite, it has hitherto not been possible to attack the causal factor.

Using the spirochaetal stain evolved by him, Lennhoff has succeeded in demonstrating organisms resembling spirochaetes in biopsy specimens taken from the erythematous lesions. With a view to the possibility of the spirochaetes demonstrated being the casual factor, according to Lennhoff's directions groups of erythema migrans cases have been treated with spirochaeticides at the St. Göran's Hospital, Karolinska Sjukhuset, and Stockholm South Hospital. The series comprises 16 patients with typical erythema chronicum migrans.

CASE REPORTS

Case 1. - Man aged 44, record Nr. 13671/46 (St. Göran's Hospital). Duration 3 months. No statement as to tick bites. 21/11 1946. Iodobismitol 2 ml. 28/11. The eruption has practically disappeared. Iodobism 2 ml.

Case 2. - Boy aged 5, record Nr. 1773/47 (St. Göran's Hospital). Since the middle of July, 1946, an eruption spreading concentrically in the sacral region. On 19/10 an erythematous area the size of a palm and circular in shape was noted by the attending physician, who suspected a tick bite and predicted further spread of the lesion. After extending over half the dorsum and down on to the thighs, according to the mother's statement the circle turned pale but was replaced by a less discrete erythema, which remained unchanged for more than a month. 22/1 1947. Bismuth subsalicylate 1 ml. 29/1. The erythema has nearly subsided. 6/2. Just a trace left of the erythema.

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¹For references see Hellerström, S. Acta Derm Venereol, Transactions Oslo Meeting.

Case 3. - Man aged 39, record Nr. 6381/41 (St. Göran's Hosp.). Had suffered a tick bite in September or October, 1946. In December an extending erythema was observed at the site of the bite. 10/5 1947. Typical erythema migrans involving the left half of the chest. A biopsy was made by Dr. Lennhoff, who using his HgS stain succeeded in demonstrating occasional elements resembling spirochaetes in the sections. Bismuth subsalicylate 1 ml. Patient's weight, 110 kg. 16/5 Bism. subsal. 1 ml. 21/5. Peripheral spread of the erythema. Bism subsal. 1 ml. 27/5. Central subsidence but upward extension, viz. to upper margin of left nipple. Bism. subsal. 2 ml. 7/6. Upper border of erythema now 2 cm. above left nipple. Bism subsal. 2 ml. 14/6. Bism. subsal. 2 ml. 28/6. Upper border, now manifested by a slightly erythematous zone 4 cm. above left nipple. The lower portion of the erythema has disappeared. Bism. subsal. 2 ml. 5/7. Upper border 5.6 cm. above the nipple. Bism. subsal. 2 ml. 2/8. 7 cm. above the nipple. Bism. subsal. 2 ml. + neoarsphenamine 0.6 g 9/8. No appreciable erythema. Bism. subsal. 2 ml. + neoarsphen. 0.6 g. 2/8. 7 cm. above the left nipple a festoon-shaped erythema of 10 cm. in length. Bism. subsal. 2 ml. + neoarsphen. 0.6 g. 13/9. Condition unchanged. 4/10. Slight spread of erythema, most clearly apparent on the back. Bism. subsal. 2 ml + neoarsphen. 0.6 g. 8/10. According to the information received from the patient, no visible erythema. 11/10. Still no visible erythema. Bism. subsal. 2 ml. + neoarsphen. 0.6 g. 18/10. The erythema has recurred within a very small area. Bism. subsal. 2 ml. 15/11. The erythema has completely disappeared from the anterior aspect of the chest, whilst a slight trace still remains in the right half of the back. Bism. subsal. 2 ml. + neoarsphen. 0.6 g. 29/11. The erythema has entirely disappeared. Bism. subsal. 2 ml. (16th injection) + neoarsphen. 0.6 g. (7th injection).

Case 4. - Man aged 67, record Nr. 9851/47 (St. Göran's Hosp.). No history of tick bite but exposure during the summer. 13/8 1947. Discrete erythema, treated with a mild ointment. 19/8. The erythema has extended, viz. 12 by 13 cm. Bism. subsal. 2 ml. 23/8. Bism. subsal. 2 ml. 29/8. Bism. subsal. 2 ml. 2/9. The erythema has disappeared.

Case 5. - Man aged 27, record Nr. 12137/47. (St. Göran's Hosp.) 1/10 1947. No statement as to insect bites. Typical erythema migrans. Iodobism. 2 ml. 4/10 Iodobism. 2 ml. 8/10. Erythema paler. Iodobism. 2 ml. 11/10. Iodobism. 2 ml. 15/10. Iodobism. 2 ml. 18/10. Iodobism. 2 ml. 23/10. Iodobism. 2 ml. 1/11. The erythema has disappeared. Iodobism. 2 ml. 8/10. Erythema paler. Iodobism. 2 ml. 11/10. Iodobism. 2 ml. 15/10. Iodobism. 2 ml. + neoar-

sphen. 0.6 g. 12/11. Erythema unchanged as to size but paler. *Iodobism. 2 ml. + neoarsphen. 0.6 g. 15/11.* Erythema scarcely visible. *Iodobism. 2 ml. + neoarsphen. 0.6 g. 22/11.* No visible erythema. *Iodobism. 2 ml. (12th inj.) + neoarsphen. 0.6 g. (4th inj.) 29/11.* There is just a slight trace of discoloration occupying a small portion of the site previously involved by the erythema.

Case 6. - Man aged 62, record Nr. 9902/47 (St. Göran's Hosp.). No history of insect bite. 13/8 1947. Typical erythema migrans, treated with a mild ointment 3/10. The erythema has spread. *Iodobism. 2 ml. 7/10. Iodobism. 2 ml. 23/10.* Erythema unchanged. No treatment. - Defaulter.

Case 7. - Women aged 48, treated in private practice. Had suffered a tick bite in the left popliteal fossa toward the end of July or early in August, 1947. 24/10 1947. Typical erythema chronicum migrans measuring roughly 3 dm. in diameter. *Iodobism. 1.5 ml.* 7 days later the erythema had paled very considerably. 6/12. Just a trace of discoloration. *Bism. subsal. 1.5 ml.* According to the patient's statement, a couple of days later the eruption had entirely disappeared showing up once more about new year's day, however, when the patient observed an upper margin of about 5 cm. in length, which a week later was followed by a short lower border. 25/3 1948. Complete, closed circle, now with a diameter of approximately 5 dm. *Mapharside 0.06 g. 26/3.* The erythema has paled. 31/3. Now just discernible discoloration. *Maphars. 0.06 g.* Nausea. 6/4. *Bism. subsal. 1 ml. 9/4.* No skin lesions, but the patient states that in the morning, when she was having a hot bath, the erythema showed up with a somewhat elevated border. 14/4. Slight but not clearly visible erythema. *Bism. subsal. 1.5 ml. + neoarsphen. 0.45 g.* Nausea. 23/4. Only upper border of erythema clearly visible. *Bism. subsal. 1.5 ml. + maphars. 0.06 g.* Vomiting and diarrhoea. 3/5. Poorly visible upper erythematous border. *Iodobism. 2 ml. 12/5.* Condition unchanged. *Iodobism. 2 ml. 16/5.* Toxoplasmosis test, negative. There is just a suggestion of an erythematous margin.

Case 8. - Man aged 27, record Nr. 13270/47 (St. Göran's Hosp.). Tick bite in July, 1947. 28/10 1947. Typical erythema migrans. *Iodobism. 2 ml. 1/11.* No appreciable change. *Iodobism. 2 ml. 6/11.* Erythema still unchanged. The patient declines further treatment.

Case 9. - Woman aged 53, record Nr. 7343/48 (St. Göran's Hosp.). Had suffered a tick bite in the right breast in July, 1948. 31/8 1948. Typical erythema migrans slightly larger than a palm on the right breast. Itching and intermittent stinging pain. *Mild ointment, penicillin 450 000 units* (in oil and wax). 16/9. The itching and pain have abated. *Penic. 450 000. 8/9. Penic. 450 000. 16/9.* The subjective symptoms have subsided. A small patch still remains of the erythema.

Case 10. - Man aged 36, record Nr. 6551/48 (Karol.

Sjukh.). Since July, 1948, erythema migrans around the left nipple following tick bite. 4/11 1948. Typical erythema migrans circle over the right half of the chest. *Iodobism. 1 ml. 9/11. Iodobism 2 ml. 15/11. Iodobism. 2 ml. 19/11.* Two day ago the erythema disappeared. *Iodobism. 2 ml. 23/11. Iodobism. 2 ml. 27/11.* Erythema as conspicuous as prior to the injections. *Iodobism. 2 ml. 11/12.* The erythema has entirely disappeared. 31/1 1949. Still no visible skin lesion, but the patient complains of slight intermittent stinging pain at the site previously involved.

Case 11. - Women aged 49, record Nr. 2657/48 (Karol. Sjukh.). Tick bite on the right thigh in September, 1948. A fortnight later migrating erythema around the site of the bite. Early in November erythema also on the right forearm and, since 14/11 1948, around the left nipple. 16/11 1948. Spinal puncture, Pandy, weakly positive; Nonne, weakly positive; Mastix, I, I, 0, 0, 0, 0; total proteins, 17.88; globulin, 7.09; albumin, 10.79; ratio globulin/albumin, 0.66; monos. 16; reds 3/mm³. *Neoarsphen. 0.3 g. 14/1 1949.* The patient on request returned for examination. The three erythema circles have somewhat extended. The borders are rather diffuse on the leg and arm but well defined on the left breast. *Neoarsphen. 0.6 g.* Vomiting. 18/1. *Maphars. 0.06 g. in lactose solution.* Vomiting. 21/1. No skin lesions visible on the leg and arm but still present, though with diffuse margins, on the left breast. *Penic. 300 000 units (in oil and wax).* 25/1 No visible erythema. *Penic. 300 000 units.*

Case 12. - Women aged 62, record Nr. 2683/48 (Karol. Sjukh.). Early in June, 1948, the patient suffered a tick bite beneath the left breast. In the middle of October a fairly discrete erythema developed on the right calf, and early in November a small erythematous area appeared on the left upper arm. No pain, no itching. Headache in October, persisting until after the 1st injection. 18/11 1948. Spinal puncture, Pandy, negative; Nonne, negative; Mastix, negative; total proteins, 26.01; globulin, 5.13; albumin, 20.88; ratio globulin/albumin, 0.25; monos. 2/1 ml. *Procaïn-penic. 300 000 units. 22/11.* Borders diffuse. The erythema has paled. *Procaïn-penic. 300,000 units. 31/11.* Just a slight trace of erythematous margins. 9/12. The erythema has entirely disappeared.

Case 13.¹ - Man aged 22, record Nr. 1760/49 (Stockholms South Hosp.). Towards September the patient spends three months in camps, and during the period, October - December 1948, he has every Sunday done voluntary work cutting timber. Previously healthy. Did not note tick bites. Headache since early in December, at the same time erythematous skin lesion in the upper portion of the left thigh. No itching, no fever. Slight giddi-

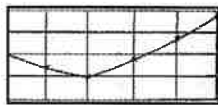
¹In 1949 this case was presented by Dr. Leczinsky at the February meeting of the Swedish Dermatological Society.

ness. The skin lesion showed circular extension and central subsidence. On 3/1 1949 the patient saw a physician and was given tablets for the headache, no benefit. Since 6/1 nausea and vomiting after meals, was unable to retain any food. On 17/1 he was admitted to the Stockholm South Hospital, where Dr. Bäfverstedt made a diagnosis of erythema migrans with meningitis. Physical examination, urinalysis, and hematology, no abnormality. Pulmonary and cardiac skiagrams. N.A.D. Ekg., normal. Ocular fundi, N.A.D. Skin findings: In the upper portion of the right thigh a festoon-shaped, slightly elevated erythematous zone, measuring roughly one centimetre across and extending from the groin downward over the medial aspect of the thigh, its anterior aspect, and then turning on the lateral aspect towards the trochanteric region. In both groins firm, non-tender lymph nodes of bean size. Neurology, appreciable nuchal rigidity, Kernig's and Lasègue's signs at 45° positive in either leg, otherwise N.A.D. A biopsy, as was to be expected, showed a rather uncharacteristic histological picture. Biopsy material ground in a mortar, suspended in normal saline, and injected intradermally into a human subject, failed to evoke a response (period of observation, four months).

17/1. Spinal puncture:

W.r., negative	Pandy ++
Meinicke's clarification test, negative	Nonne ++(+)
Müller's conglobation test, negative	Weichbrodt +
1 ml. = 100 cells	
monos. 1140	
polys. 60	
reds 20/mm ³	

Estimation of protein fractions according to Izikowitz: Total proteins, 169.91; globulin, 42.83; albumin, 127.08; ratio, 0.34. Markedly pathological rates of total proteins, globulin, and albumin, but a normal ratio (meningitis type, yet not syphilitic, the ratio as a rule also showing considerable elevation in syphilis cases according to Flodén).



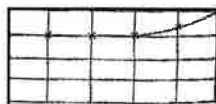
18/1, 12 o'clock. *Penic.* 30 000 units at 3-hour intervals; 6 p.m. 60 000 units at 3-hour intervals. 19/1, 6 o'clock. 75 000 units at 3-hour intervals; 9 o'clock, 100 000 units at 3-hour intervals. 20/1. Striking subjective improvement. No headache, no nuchal rigidity. Lasègue's sign 60° in either leg. Just a slight trace of erythema.

25/1. Spinal puncture:

Fluid colourless, clear	
Nonne, trace	Pandy (+)
Weichbrodt (+)	
Cells: polys.	22
monos.	171
reds	14 (fresh)

21/1 *Penic.* 100 000 units 6 times daily until a total of 10 000 000 was reached on 1/2.

28/1. Apyretic during the whole period. The erythema has disap-



peared. No nervous symptoms.

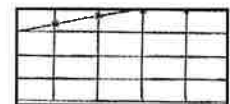
3/2 Spinal puncture:

Fluid clear	
Pandy (+)	
Nonne, trace	
Weichbrodt (+)	
Cells: polys.	10
monos.	42
reds	2/mm ³



17/2. Spinal puncture:

Pandy +	
Nonne, trace	
Weichbrodt (+)	
Cells: polys.	6
monos	17
reds	15



Case 14. - Women aged 34, record Nr. 9280/48 (St. Göran's Hosp.). In the summer of 1948 itching all over the body. The attending physician, suspecting scabies, prescribed an antiscabious lotion and subsequently ammoniated mercury ointment. 22/11 1948. Oozing in the umbilical region. Typical erythema migrans on both breasts and right upper arm. (During the summer the patient had suffered a tick bite.) 22/11. *Penic.* 450 000 units (in oil and wax). 23/11. The itching has abated, the dermatitis in the umbilical region improved. *Penic.* 450 000 units. 29/11. Still further improvement of the dermatitis in the umbilical region. The erythematous lesions have disappeared. 9/12. Skin, perfectly normal.

Case 15. - Women aged 45, record Nr. 517/49 (Karol. Sjukh.). 31/1 1949. In 1948, viz. in the summer, the patient had suffered a tick bite in the right upper arm, where a typical erythema migrans is now observed. A week prior to this bite she had been bitten by a tick lower down in the same arm, but without local erythema ensuing. W.r., negative. Sedimentation rate, 30 mm./1 hour. Blood count, eosinophilia of 6%, otherwise N.A.D. Material taken from the erythematous border was ground in a mortar and injected intradermally into two subjects without evoking erythema (period of observation, 4 months). 1/2. Spinal puncture, no abnormality. 2/2. *Procaïn-penic.* 900 000 units. 3/2. *Procaïn-penic* 900 000 units. 4/2. Erythema paler. *Procaïn-penic.* 900 000 units. 5/2. *Procaïn-penc.* 600 000 units. 7/2. No inflammation is felt on palpation. The erythema is scarcely visible. 10/2. The erythema is hard to discern. 15/2. Condition unchanged. 23/2. Only the lower border to be discerned on very careful inspection. The biopsy scar is enclosed in normal skin. 1/3. Findings the same as on last examination. 5/4. No changes visible.

Case 16. - Women aged 38, record Nr. 1520/49 (St. Göran's Hosp.). Has not noted a tick bite. Migrating erythema since December, 1948. 2/2 1949. Feels weak in one arm (decrease in muscular force). *Penic.* 450 000 units.

3/2. Spinal puncture: Pandy + , Nonne - , cells: polys. 19, monos. 13, reds 271 per 1 mm.³, Mastix, negative. *Penic.* 450 000 units. 4/2. *Penic.* 450 000 units. 5/2. *Penic.* 450 000 units. 7/2. The erythema has disappeared. *Penic.* 450 000 units. Brachial muscular force, normal.

In eight cases, i.e. in one-half of the series, the outpatient records pertaining to instance of erythema migrans contain statements as to tick bites.

A patient presented three separate erythematous lesions, another one two, and the remaining one each.

The spinal fluid was examined of five patients (Cases 11, 12, 13, 15, 16), three of whom (11, 13, 16) presenting pathological changes in the form of increased cell content, viz. 16 monos., 1 140 monos. + 60 polys., and 13 monos. + 19 polys. respectively. Case 13, i.e. that with the high rise in cells, also had considerably elevated albumin and globulin rates in the C.S.F. In Case 11 there were neither nervous system damage nor subjective discomfort, Case 13 presented frank meningitis, and in Case 16 the muscular force was impaired in one arm. One of the two patients without C.S.F. abnormality had for about a month been inconvenienced by aetiologically obscure headache subsiding on institution of treatment.

According to the drugs used in treatment, the present series can be divided into four groups as follows: *Group I*, only iodobismutol (JBi) or bismuth subsalicylate (Bi); *Group II*, both bismuth (JBi, Bi) and neoarsphenamine (Neo) and/or mapharside (Maph); *Group III*, neoarsphenamine, mapharside, and penicillin; *Group IV*, only penicillin. [see Table]

Of the six patients treated solely with bismuth (Group I), two defaulted after two injections. At that moment their erythema did not show any effect of the treatment. Of the remaining four, two presented quite inconspicuous residues of the erythema 7 and 13 days after respectively after a single injection. In the two other patients treated with 3 and 6 injections respectively, the erythema had disappeared definitely 13 and 37 days after institution of treatment. In the latter cases temporary disappearance during time of treatment was observed to precede the definite subsidence of the erythema.

Group II comprises three patients initially treated with bismuth salts. The bismuth doses being small in relation to the body weight and the treatment interrupted for considerable periods, only a partial and temporary disappearance resulted of the erythema. Neoarsphenamine or mapharside was then resorted to. Not until 6 1/2 and 2 months respectively after institution of treatment was freedom from symptoms attained in two of the cases. As regards the third patient (Case 7), there was marked improvement after the first bismuth injection and temporary freedom from symptoms after the second one administered 6 week later; when recurring, however, the erythema was more extensive than

previously, an observation made also in another case or two. Neoarsphenamine and subsequently, mapharside were adopted as supplementary treatment but owing to intolerance symptoms had to be abandoned. 6 1/2 months after the first bismuth injection the patient still presented a small remnant of the erythema.

Group III consists of just one case with three erythema-migrans circles. At the outset we had intend to use neoarsphenamine only. However, after the first injection the patient defaulted, returning two months later on being requested to do so. The erythema circles had somewhat migrated. Vomiting ensued from a single neoarsphenamine or mapharside injection, this type of treatment was discarded. Three days after the latter injection two of the circles had disappeared, a penicillin injection then being given. Four days later there was complete freedom from cutaneous symptoms.

Six cases, Group IV, were treated with penicillin alone, viz. from 600 000 to 10 000 000 units. In one case complete freedom from symptoms did not ensue until 2 months after institution of treatment, but four patients were rendered symptom-free with 3 weeks, whereas one after this period presented a coin-sized remnant of the erythema. Of particular interest is the action of penicillin on the neuro-meningeal symptoms sometimes associated with erythema migrans. In one patient (Case 12) who during the last few months before treatment had suffered from headache but did not present C.S.F. changes, the headache yielded to the first injection of penicillin. Another patient (Case 16) complained of weakness in one arm; there was a decrease in muscular force in the arm affected and a rise in cells in the C.S.F. After four penicillin injections (1 800 000 units) the subjective discomfort and objective brachial symptoms had entirely subsided (the C.S.F. was not re-examined). The only patient who was hospitalized and thus could be carefully observed, and who presented frank symptoms of meningitis, under penicillin treatment (10 000 000 units) showed an extraordinary prompt, both subjective and objective, improvement (see Case 13).

The therapeutic results achieved indicate that in cases of erythema migrans disappearance or improvement of cutaneous symptoms can be brought about by bismuth salts alone. If the dosage is insufficient, the erythema may pale down only partly or disappear temporarily. This seems to apply also to the arsenicals. The most rapid therapeutic effect will apparently be attained by administering penicillin. According to the experience derived from the treatment of early syphilis, penicillin seems to be out most powerful spirochaetocide. The prompt effect of each separate injection was frequently striking, considering all the types of penicillin. In the few cases of erythema migrans presenting symptoms of neuro-meningeal involvement and treated with penicillin, the action of the

Table

Divided Up Into Injections			
Case Nr.	Totals	Nr.	Results of Treatment
Group I			
1	JBi 2 ml. + (2 ml.) ¹	1	7 days after institution of treatment the erythema had practically disappeared.
2	Bi 1 ml.	1	Disappearance of erythema after 13 days.
4	Bi 6 ml.	3	Disappearance of erythema 13 days after institution of treatment.
6	JBi 4 ml.	2	After 20 days condition unchanged. (Treatment abandoned).
8	JBi 4 ml.	2	After 9 days condition unchanged. (Treatment abandoned).
10	JBi 11 ml.	6	Temporary disappearance of erythema during treatment, definite 37 days after the 1st injection.
Group II			
3	Bi 29 ml.	14	Temporary disappearance of erythema during treatment, definite after 6 1/2 months
	Neo 3.6 g.+(Bi 2 ml. Neo 0.6g.) ¹	6	(Patient's weight, 110 kg. Long interruption of treatment.)
5	JBi 24 ml.	12	Temporary disappearance of erythema during treatment; 2 months after the 1st injection
	Neo 2.4 g.	4	still very slight discoloration.
7	JBi 5.5 ml.	3	Temporary disappearance of erythema during treatment; roughly 6 1/2 months after the
	Bi 7 ml.	5	1st injection just a trace of erythematous border. (Long intervals between the first few
	Neo 0.6 g.	1	injections.)
	Maph. 0.25 g.	4	
Group III			
11	Neo 0.9 g.	2	Disappearance of all the erythematous lesions about 9 weeks after institution of treat-
	Maph. 0.06 g.	1	ment. (Disappearance of two erythematous circles prior to institution of penic. Com-
	Penic. in oil and wax	1	plete freedom from symptoms 4 days after the penic. injection.)
	300 000 units		
	+ (300 000 units) ¹		
Group IV			
9	Penic. in oil and wax	2	Coin-sized erythematous residue 16 days after institution of treatment.
	1 350 000 units		
12	Procain-penic. 600 000 units	2	Disappearance of erythema 20 days after the 1st injection
13	Penic. 10 000 000 units	105	Disappearance of erythema and nervous symptoms with 10 days after institution, and
			prior to termination, of treatment. Gradual improvement of the C.S.F. changes.
14	Penic. in oil and wax	2	Disappearance of erythematous lesions 7 days after institution of treatment.
	900 000 units		
15	Procain-penic.	4	Disappearance of erythema within 2 months after the 1st injection.
	3 300 000 units		
16	Penic. 1 800 000 units +	4	Disappearance of erythema 5 days after the 1st injection (penic. administered on four
	(450 000 units) ¹		consecutive days).

¹Injection given on last day of observation or after disappearance of erythema.

drug was highly gratifying on both the C.F.S. changes and other signs of meningeal and nervous disease, objective symptoms as well as subjective discomfort.

The erythema itself may be allergically conditioned. Evidence in favour of this conception is afforded by the positive result of intradermal tests with tick extract as obtained by Hellerström and subsequently verified by Dalsgaard-Nielsen and Kierkegaard, and by the observation that the erythema is apt to disappear with an area exposed to quartz light, and to become visible again when it has migrated beyond the limits of the area irradiated.

The idea of the condition being purely allergic, however, is discouraged by the satisfactory therapeutical action

of the drugs used in the present case series, since these drugs are devoid of anti-allergic properties.

The therapeutical results achieved with penicillin indicate that erythema migrans is infectious in nature, and the effects of all the drugs used in treatment, in particular the bismuth salts and neoarsphenamine, tend to suggest a spirochaete as the causative organism. Definite evidence is still lacking in this respect, but the therapeutical results in conjunction with Lennhoff's findings of spirochaetes in histological sections prepared from lesions of erythema migrans and with the demonstrated presence of spirochaetes in ticks, render probable that a spirochaete is the infective agent.

The infectious aetiology of erythema chronicum migrans, on the other hand, is not definitely adverse to the possibility of the cutaneous lesions being allergically conditioned. The erythema is perhaps due to an organism, most frequently deriving from ticks and possessing sensitizing power, which is introduced into the skin.

The negative results of inoculation test may be due to the material for inoculation having been taken from the circumference of the erythematous circle possibly arising through an allergic mechanism; in addition, the infection may require a certain predisposition.

SUMMARY

An account is given of sixteen cases of erythema

chronicum migrans Afzelius treated with bismuth, neoarsphenamine, marpharside, and penicillin, either separate or in various combinations. In 14 cases (two patients defaulted) the therapeutical action upon the erythema was unmistakable and sometimes very rapid. If the dosage was insufficient, or if there were long intervals between the injections, the erythema was apt to pale down only partly or disappear temporarily. Penicillin appeared somewhat superior to the other drugs used, entailing a highly gratifying curative effect in a case with frank meningitis. The aetiology is discussed of the condition, special attention being given to the conclusions possibly to be drawn from the good therapeutical results.

Penicillin Treatment of Erythema Chronicum Migrans Afzelius

Einar Hollström

In 1946 the first attempts were made to treat erythema chronicum migrans (E.M.) with spirocheticides (Hollstrom, E., *Acta. Derm. Ven.*, 1951, 31, page 235). The impetus to this therapeutic trial had been given by Lennhoff's findings of spirochetes or spirochetoid organisms in skin presenting E.M. changes. As was found, rapid cure could be achieved with arsphenamine, bismuth, and penicillin. The erythema disappeared, but it recurred if the dosage had been insufficient. Of the drugs given, penicillin was found to be the most effective and, the experience having meanwhile accrued, was later used throughout. Penicillin proved particularly beneficial in cases with supervenient-serous or purulent-meningitis.

THE MATERIAL

From 1948 onwards to and including 1957, at the Department of Dermatology of Karolinska Sjukhuset 77 patients with E.M., 15 men (19.5%) and 62 women (80.5%), had been treated with penicillin. The age of the patients ranged from 2 to 70, and the distribution among the different age groups is given in fig. 1. In 27.3% of the cases there was a history of tick bite and in 11.7% of bites of insects of unknown species. In those instances where information as to the incubation period, i.e. the time between insect and appearance of the erythema, was available, this had varied between a fortnight and 4 months.

As will be seen in fig. 2, the incidence rates of E.M. during the years, 1948-1957, show a very considerable variation. The low rates in 1948-1951 would partly seem to be due to the fact that the skin clinic of Karolinska Sjukhuset was opened in 1948, and that during the first few years the number of patients treated in the outpatient service was much lower than later on. Particularly surprising, however, is the bottom rate in 1955, when no definitely established case of E.M. was recorded. A possible explanation is, that the summer of this year was exceptionally dry, to the great detriment of plants and insects. In the next year, on the other hand, there was a strikingly high culmination.

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TREATMENT

The penicillin dosage varied between minimum 300,000 units and maximum 7,300,000 units. Generally the dosage was between 600,000 units and 2,400,000 units; thus 18 patients were given 600,000 units, 14 patients 1,200,000 units, 8 patients 1,800,000 units, and another 8 patients 2,400,000 units, that is to say 48 out of 65 (see below) were treated with one of the penicillin amounts stated. 600,000 units was administered as a single dose, whereas larger amounts were divided into injections given daily or every other day. In a few instances penicillin was given by injections as well as orally. Here, however, the totals are stated irrespective of the mode of administration.

RESULTS AND DISCUSSION

It was possible to follow up 65 cases of E.M., viz. either by means of the notes entered in the records or of supplementary information. In 12 instances the data were insufficient and no contact could be established with the patients, or these were unable to recall the course of illness.

In the assessment of the results the time required for cure was stated in weeks after termination of treatment, if daily examination of the patients was not feasible. In a proportion of the cases the erythema disappeared before the treatment was completed; none the less these instances were referred to the group, Cure within 1 week, after termination of treatment. Sometimes a weak brownish pigmentation remained when the erythema had subsided, but this was not included in the time required for cure.

Cure within 1 week after treatment:	34=52.3%	} 89.2%
" " 2 weeks " "	: 24=36.9%	
" " 3 weeks " "	: 5=7.7%	
Recurrence		=3.1%

Hence, in more than one-half of the series the erythema disappeared within 1 week and in 89.2% within a fortnight. The two recurrences were observed in children. One of them aged 5, was given 300,000 units penicillin, whereupon the erythema disappeared within 1 week. After 4 weeks the patient was still free of symptoms, but after another 2 weeks the erythema returned. 300,000 units penicillin was then administered once more and produced cure without further recurrence. The other child, aged 9, did not present any signs of E.M. 1 week after treatment with 600,000 units penicillin. Three weeks later there was a recurrence, which was treated with 1,200,000 units penicillin, definite freedom of symptoms resulting within 1 week. Since, accordingly, recurrences may occur after 600,000 units, totals larger than this dose are recom-

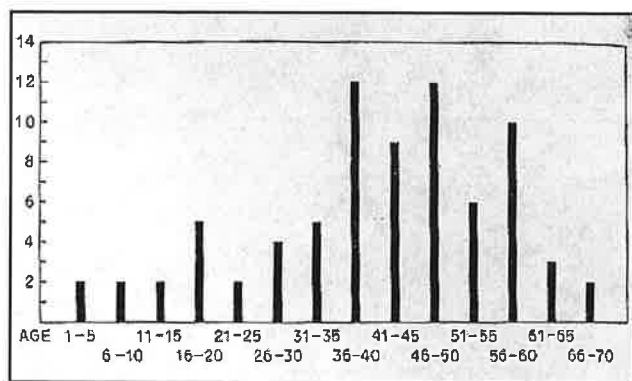


Figure 1.

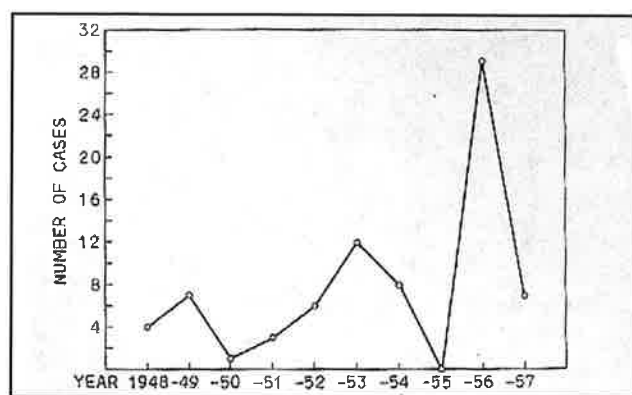


Figure 2.

mended, say 1,200,000 units or possibly even more, the latter, naturally, in cases with complications such as meningitis etc.

Prior to the therapeutic trial with spirocheticides including penicillin there was no efficient treatment: the erythema spread over the entire body surface with central clearing. The whole integument having been affected, immunity was generally thought to exist. As E.M. is rapidly cured by penicillin, the formation of antibodies will probably be interrupted, analogously to what is the case in penicillin treatment of scarlet fever. It is thus to be expected that a patient suffering from E.M. and having been treated with penicillin may develop the disease afresh. Such a case is actually included in my material.

The patient was a woman who in 1952 presented typical E.M. following insect bite. She was cured after treatment with 600,000 units penicillin. In 1957 she had the same disease again, although without a history of insect bite. Also at that time 600,000 units penicillin produced cure with 1 week.

Judging by the favourable results of penicillin treatment an infectious aetiology of E.M. would seem to be highly probable. In order to secure evidence in this respect I have tried to transfer the disease to healthy subjects, viz. by injecting minced tissues from three patients with E.M. into ten volunteers, but without positive result. In addition experiments were carried out in which blood of E.M. patients was injected, also these without result. Similar experiments have even been performed by other workers without success. Possibly a special disposition towards the disease is a necessary condition for its development.

The present study shows that (i) penicillin has proved an excellent remedy for erythema chronicum migrans, but that (ii) with insufficient dosage (in these instances 600,000 units or less) recurrence many occur, that (iii) an infectious aetiology is likely but that transfer experiments were unsuccessful, and that (iv) definite or permanent immunity does not always exist after penicillin treatment, but that the patients may develop the disease afresh.

SUMMARY

A ten-year material of erythema chronicum migrans was studied, which during the period, 1948-1957, had been treated with penicillin in the outpatient service of the Department of Dermatology of Karolinska Sjukhuset. In 89% of 65 cases the erythema disappeared with a fortnight. A recurrence was noted in only two cases, i.e. 3% after penicillin doses of 600,000 and 300,000 units respectively. Penicillin has thus proved an admirable therapeutic agent, and 1,200,000 units or possibly a somewhat higher dosage is advised for even uncomplicated cases. One patient had the disease twice at an interval of five years, which is supposed to be due to the fact that the penicillin treatment interrupts the immunization. An infectious aetiology is considered likely, but all transfer experiments were unsuccessful.

Erythema Chronicum Migrans

Rudolph J. Scrimenti, MD

To my knowledge, this is the first case of erythema chronicum migrans in the United States. Eruption and radicular pain followed a wood tick bite. Treatment with benzathine penicillin G (Bicillin) was curative.

A migrating erythema with systemic symptoms resulting from a tick bite is unusual in the United States. Our knowledge of this curious condition comes from European reports. This toxic, circinate skin eruption advances peripherally and is occasionally associated with neurological symptoms. The cause is uncertain. However, some believe it to be an infectious agent, perhaps a spirochete or rickettsia, possessing allergenic properties.^{1,2} Ticks transmit the disease although other arthropods may be vectors.^{3,4} It is not known whether the neurological manifestations are infectious, toxic or allergic. The purpose of this communication is to reawaken interest in this obscure but classical condition, known for over a half a century, which is now readily curable.⁵

REPORT OF A CASE

In January 1969, a 57-year-old physician had chronic erythema of the right side of the torso which was unresponsive to flurandrenolide (Cordran). A recent hospitalization failed to reveal any cause for his complaints of headache, malaise, and dull pain radiating over the right hip. Periodic, low-grade fever accompanied the skin eruption.

An annular area of edema and erythema was present, extending from the mid-chest to mid-back and encircling the right axilla and iliac crest. The dermatones innervated by T-12 and L-1 were hyperesthetic. Above the iliac crest there was a tender, punctate area of redness and induration. The patient stated this was the site of a wood tick bite sustained three months previously while grouse hunting in north central Wisconsin (Medford). He recalled that after removing the tick from the skin, a nickel-sized welt appeared at the bite site. It slowly spread peripherally, cleared centrally, and culminated in the larger circular area now present. A morbilliform eruption of the upper part of the torso appeared shortly after the bite, but vanished within one week while the patient took a combination antihistamine decongestant (chlorpheniramine

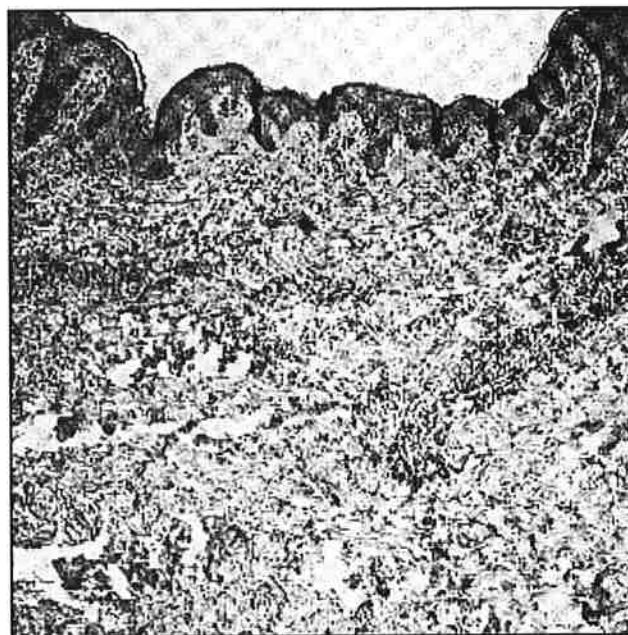


Figure 1. Low-power view of tick bite. Epidermis is unremarkable. Mixed leukocytic dermal infiltrate. No tick parts are identified. Bacteria not demonstrated (x4).

maleate, phenylpropanolamine hydrochloride, and isopropamide iodide [Ornade]. It has not recurred.

The bite site was biopsied, and, surprisingly, all symptoms subsided for 24 hours only to return with increased intensity.

The histological changes showed a dermal leukocytic infiltrate arranged about the appendages. The tissues surrounding the infiltrate were slightly edematous. Foreign material was not seen. Spirochetes were not demonstrated with silver stains (Fig 1 and 2).

Lipoprotein electrophoresis showed a type IV pre-B hypertriglyceridemia. Electrocardiogram and roentgenogram of the chest were normal. Normal values were found for the following: complete blood cell count, differential cell count, serum electrolytes, carbon dioxide, fasting blood sugar, protein bound iodine, creatine, blood urea nitrogen, bilirubin, cholesterol, lactic dehydrogenase isoenzymes, calcium, phosphorus, serum transaminase, total serum proteins, albumin, and the venereal disease research laboratory test for syphilis. The *Proteus* OX₁₉ (serologic) test was negative.

Treatment consisted of the administration of 1.2 million units of benzathine penicillin G (Bicillin) intramuscu-

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From the Department of Dermatology, Marquette School of Medicine, Milwaukee.

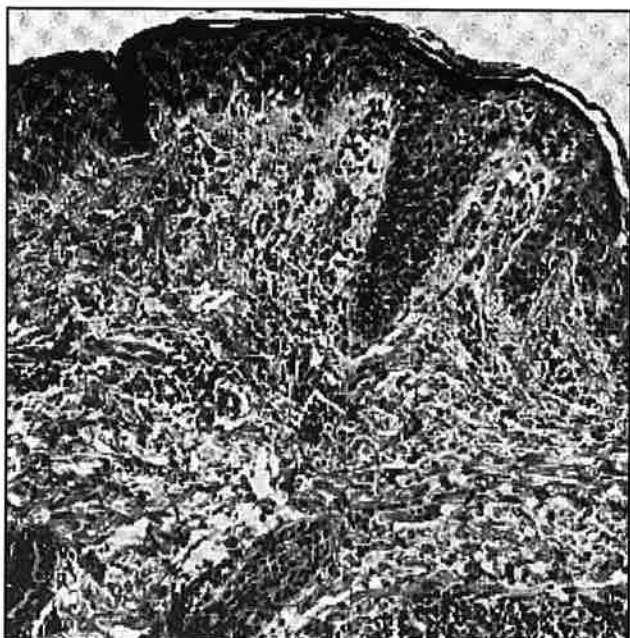


Figure 2. Higher power magnification of tick bite. Lymphocytic and plasma cell periadnexal infiltrate is shown. Tissues about inflammation are slightly edematous (x25).

larly. The patient became symptom-free within 48 hours. There has been no recurrence of symptoms for the past year.

COMMENT

Although specific organisms could not be incriminated, the patients' clinical course and response to therapy suggest that erythema chronicum migrans is a low-grade infection. Why it so rarely complicates so common an occurrence as arthropod bites remains an enigma. A search of the American literature failed to uncover a similar case in the United States.

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Lyme Disease Redux: The Legacy of Sven Hellerström

Rudolph J. Scrimenti, MD and Mark Scrimenti

In his article "Discovery of the Lyme Disease Spirochete: A Historical Review,"¹ Dr. Willy Burgdorfer recounts the clinical and epidemiological developments leading to his "unexpected" discovery in 1982 of the long-sought cause of erythema chronicum migrans (ECM) and Lyme disease. He credits a paper, written more than 30 years earlier by Dr. Sven Hellerström, of the Karolinska Institute in Stockholm, with providing essential clues in making this discovery.

"I remember the European literature," Burgdorfer wrote, "particularly Dr. Hellerström's paper ... and I could not dismiss the thought that (the information contained therein along with the 'accidental' discovery of spirochetes in the midgut of two female ticks) had led me to the discovery of the long-sought cause of ECM and Lyme disease."¹

The paper in question, entitled "Erythema Chronicum Migrans Afzelius with Meningitis," was presented by Dr. Hellerström at the 43rd annual meeting of the Southern Medical Association in Cincinnati in 1949. Willy Burgdorfer was still a graduate student in Basel, Switzerland, at the time, working on his thesis related to the East African relapsing fever spirochete.

Dr. Hellerström, who nearly two decades earlier had described the first case of ECM associated with extracutaneous symptoms—specifically meningitis—concluded his paper with the observation "...it seems reasonable to raise the question of whether the ticks are carriers of spirochetes with allergizing (and immunizing?) properties."²

He also furthered interest in spirochetal research by reporting that "spirochetoid bodies have been demonstrated in material taken (by Dr. Lenhoff) from (ECM) eruptions,"³ even though these "bodies" were later determined to be artifacts.

Indeed, it was this same paper, subsequently published in *The Southern Medical Journal*, that first caught my attention as a medical student in Milwaukee around 1958. What interested me most about Dr. Hellerström's findings at the time was the possibility of diagnosing, and perhaps even treating, multi-system disorders on the basis of observable skin manifestations. As I was yet undecided as to which medical specialty I would enter, Dr. Hellerström's description of the visual detective work



Dr. Sven Hellerström, 1901-1977

involved in diagnosing patients with ECM with meningitis influenced my decision to consider dermatology. It also kept me on the lookout for similar cases.

Thus, some 11 years later, in January 1969 when a 57-year-old physician walked into my office complaining of headache, muscle pain, low grade fever, radicular pain, fatigue, and malaise in conjunction with a chronic erythema encircling the right side of his torso (from hip, around the shoulder and back again) I immediately recognized the signs and symptoms of ECM.

What really brought home this diagnosis in my mind was the patient's detailed description of a tick bite preceding the illness. The tick, removed by the patient himself, was said to be "small and engorged." Although I referred to it generically as a "wood tick" in initial reports, we now know that *Ixodes dammini*, the Lyme disease vector, was first known to be present in Wisconsin around that time.³ Remembering that the Swedes had been successful in treating this disease with penicillin, I administered intramuscular injections of benzathine penicillin G

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(bicillin) and the patient was symptom-free within a short period of time. He remained free of sequelae until his death, 2 decades later.

Soon, I tried contacting Dr. Hellerström to share this exceptional news with him, but he was too sick at the time to respond personally. Instead his wife, Gudrun, wrote me a brief letter informing me that her husband had received my communication and had encouraged me to write up the case, which proved to be the first of its kind in the United States. My article, "Erythema Chronicum Migrans," appeared in the July 1970 issue of *Archives of Dermatology*.⁴

It wasn't until several years later that the first reports of what was thought to be a new disease—a form of inflammatory arthritis—began turning up in Lyme, Connecticut. (Inflammatory arthritis had been described in relation to ECM in Europe as early as 1934,⁵ though this was not emphasized in the European literature.) In time, "Lyme arthritis," as it was initially known, came to be associated with the tick bite and the telltale circular rash, as well as other systemic symptoms. Clinical evidence continued to suggest a direct link between Lyme disease and the classical, most often curable condition known for over half a century in Europe as ECM. Meanwhile, the contributions of Hellerström and the Europeans in general were largely overlooked in the American literature.

Thus, it pleased me greatly when Dr. Burgdorfer, upon discovering the Lyme disease spirochete, acknowledged Dr. Hellerström's influence. As chair and professor of dermatology at the Karolinska Institute, Dr. Hellerström not only helped to make possible our current understanding of ECM and Lyme disease, but also served as an editor of *Acta Dermato-Venereologica* (the journal of Scandinavian dermatology), deputy director of the Karolinska Hospital, chair of the Eleventh International Congress of Dermatology, and chair of several national commissions. In short, he was a leading figure of international medicine, Swedish dermatology in particular, in the

20th century.

More importantly with regard to ECM and Lyme disease, Dr. Hellerström encouraged, supported, and readily acknowledged the individual contributions of his colleagues. Among them were Carl Lenhoff, a refugee from Nazi Germany, Einar Hollström, a departmental assistant at the time, who was inspired by Lenhoff's efforts to experiment with penicillin as a treatment for ECM. Indeed, through their mutual cooperation, these three men suggested both the origin and the cure for this international, currently widespread disease more than 40 years ago.⁶

In recent years, I have become acquainted with Dr. Burgdorfer and the two of us have discussed further developments in the field of Lyme disease research. In one of his notes to me, Dr. Burgdorfer refers to the term "Lyme disease" as a "misnomer." Like Rocky Mountain spotted fever, which today is more prevalent east of the Mississippi, Lyme disease, which now has been reported throughout much of the world, is not confined to a specific region. In this respect, perhaps the original name for this disease, ECM, or simply erythema migrans, with no geographical implications, is more apt.

Regardless, with more than 40,000 cases reported in the United States to date, "Lyme disease" has become virtually a household word here. The name Sven Hellerström, on the other hand, remains relatively unknown outside of Europe. Despite the fact that few people may recognize his name, his contributions in the field of ECM and Lyme disease research continue to benefit thousands of people throughout the world. It is this legacy that perhaps most characteristically survives him.

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