

ON THE PROVOCATIVE EFFECT OF SYNTHETIC ESTROGEN ON ERYTHEMA NODOSUM

Preliminary Report

By

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The aetiology of erythema nodosum is still obscure, but so much seems obvious, that there are several forms of provocation acting as pathogenetic factors.

- 1) Various infections, such as angina, influenza, scarlet fever etc.
- 2) The administration of specific allergens (tuberculin, trichophytin, Frei-antigen, streptococcus-antigen etc.).
- 3) Mechanical and physical factors, such as surgical intervention (e.g. on affected lymph glands), roentgen therapy, ultra-violet rays etc. Also cold, e.g. standing in ice cold water, may be considered as a provocative factor.
- 4) Chemotherapy. From earlier publications we know of iodine, bromine, salicylic acid, antipyrine, phenacetin, salvarsan and antimony. During the last few years sulfathiazole has aroused special attention.

However, the hormones also, especially the female sex hormones, somehow seem to be of importance. We know that erythema nodosum is incomparably more frequent in women than in men. The infrequency of the disorder in male adults is seen from the following Scandinavian statistics:

Mogensen 3.0 %, Skiöld 4.5 %, Rotnes 4.9 %, Löfgren 6.7 %, Ingebrigtsen 13.7 %, Mascher 14.3 % cases. Among female patients the incidence is greatest during the

years following puberty; in male patients, however, in childhood. As regards children the females do not dominate to the same extent as with adults (*Comby*: 65.9 %, *Rantasalo*: 45 %, *Roosvall*: 59.2 % girls). At the onset of puberty there is a sudden change, a rise in the female, and a decline in the male curve (*Favour & Sosman, Löfgren a. o.*).

There are observations in the literature (*Behrend, Jarisch*) indicating that the onset of erythema nodosum in women has a predilection for the premenstrual phase of the cycle, that is when the estrogen curve stands highest. *Opel* has described erythema nodosum-like eruptions appearing as a recurring menstrual exanthem in a 39 year-old "arthritic" woman. The infiltrations were atypically localized, it is true, on the face, on the right arm and on the chest, but they were accompanied by arthritic troubles in the hands and fingers. A further case of erythema nodosum in connection with the menses is given by *Gueissaz*.

Barrat & Koutseff have recently described a case of phlyctenular keratoconjunctivitis noticed 3 times in a young girl. The onset of the ocular attack became manifest each time about 48 hours before the menses. Endocrinological examination revealed symptoms of a relative hyperfolliculinia and insufficiency of the corpora lutea. The case is of interest in this connection as erythema nodosum and phlyctenular keratoconjunctivitis may be imagined as etio-pathogenetically closely related conditions.

With these cases in mind one is rather surprised not to find estrogens and stilbestrol—as far as I can see—mentioned as provocative agents in cases of erythema nodosum.

I should like to draw attention to stilbestrol in the following case report:

Case 1, doctor's wife, born 1911.

Hereditarily nothing noteworthy. No tuberculosis. Used to be healthy. Menarche at the age of 13. Aged 17, in connection with an angina, the patient had, at the beginning of November, 1928, a violent outbreak of Erythema nodosum on the lower extremities, from the ankles up to the buttocks. Tem-

perature ad 39-40° C. No symptoms from the lungs. No roentgen picture was taken on this occasion. On examination 9 years later, in 1937, the hilar shadows were enlarged, but no visible parenchymal processes were found. The tuberculin reaction was positive.

No spontaneous recurrence of erythema nodosum. She married in 1943. No children. She consulted a gynecologist in Nov. 1946. Diagnosis: *Uterus uncollis et unicornis. Cornu rudimentarium l. dx. Sterilitas primaria. Retroversio et sinistropositio uteri*. Sedimentation rate 7 mm. She was operated on, Nov. 15, 1946 (*Exstirpatio corn. rud. l. dx. et Redressio uteri*).

Synthetic estrogens (post mens.) were prescribed. She began the medication in Feb., 1947, with *Oestilben forte*, 3 tablets 3 times daily, corresponding to a daily dose of 0.0045 g diethylidioxistilbene dipropionate. About 6 days after the beginning of the course she developed erythema nodosum-like reddish infiltrations on both legs accompanied by pain, swelling and a feeling of heaviness in the legs, with rise of temperature to 37.5° C. The medication was discontinued, and the eruption disappeared within a few days, showing characteristic color changes.

A month later, after the next menstruation, a new attempt with the same stilbestrol was made, and with the same result. About 5 or 6 days after the beginning of the course, she developed similar red infiltrations as well as swelling, pain and tenderness in the legs, and the course had to be discontinued. A slight rise of temperature was noticed this time also. The infiltrations disappeared after 2-3 days, leaving dark patches which took a further 4-5 days to disappear. A third attempt at taking the tablets had to be interrupted after two days because of erythema nodosum.

The following year (1948) a new attempt at hormone treatment was made, this time with *Di-menformon*-injections, which the patient tolerated without side-effects, only a few injections being given.

In May, 1949, stilbestrol (*Stilbol*-tablets Medica) was given as an experiment; on this occasion, however, only with at most 0.005 g daily during 5 days, (0.0023 g in all). Now, also, she had a feeling of tenderness, tension, and heaviness in the legs below the knees, gradually increasing during the course and promptly disappearing when the drug was discontinued. This time no erythema nodosum-like infiltrations were noticed, probably because of the very careful administration.

The general condition of the patient was very good. Sedimentation rate 4 mm, throat and lungs healthy. On the roentgen picture in May, 1949, the hilar shadows seemed to be almost normal, or, in any case, non-contributory.

This case led me to try the effect of stilbestrol in another case of erythema nodosum. As an experimental object I had a 40 year-old woman who had recently suffered from

erythema nodosum due to sulfathiazole treatment. As the result obtained was positive, a short description of this case, too, may be indicated.

Case 2, a worker's wife, born 1908.

The patient used to be healthy. She has had no angina, no polyarthritis, nor tuberculosis. Several years ago she suffered from adnexitis, but for a long time she has had no troubles. In 1941 she had epidemic hepatitis. No menstrual disturbances worth mentioning, yet menses were latterly somewhat scarce. She has never before had erythema nodosum. She has not, as a rule, used drugs. She contends, for instance, never before having taken sulfonamides.

She was hospitalized because of an impetiginous eczema on her hands with signs of lymphangitis, and had, on Feb. 15, 1949, sulfathiazole, 12 tablets daily. On Feb. 16th she developed erythema nodosum-like reddish infiltrations on the extensor side of the left forearm. One of the lesions was about 30 mm large, the others being smaller. The medication was continued till Feb. 19th, and then interrupted when the patient had had in all 25 g sulfathiazole. This time she showed small reddish nodules, 5-10 mm in size, also on her right elbow and on the right knee. They disappeared in a few days.

The temperature was normal, throat and lungs without fault. She had three carious teeth (several teeth were missing). Sedimentation rate 38 mm. WaR —, Kahn —.

In the middle of March, 1949, stilbestrol (Stilbol forte, Medica), 0.0005 g 3 times daily was prescribed. On March 20th, having taken 0.01 g in all, the patient developed the same erythema nodosum eruption as before on the left forearm. Now, too, one of the lesions was large, the others measuring only 5-10 mm. They disappeared in a couple of days without showing any distinct change of color. Roentgenography of the lungs showed no visible parenchymal changes. The hilar shadows, however, were slightly enlarged on both sides.

DISCUSSION

The first patient was a 37 year-old married woman who, in 1928, at the age of 17, had an outbreak of erythema nodosum in connection with angina. Roentgenography in 1937 showed no parenchymal changes in the lungs, but the hilar shadows were said to be bilaterally enlarged. Because of sterility she was given 3 courses of stilbestrol in 1947. Each course, however, had to be discontinued because the stilbestrol provoked an outbreak of erythema nodosum on the legs.

If we regard erythema nodosum as being a specific infection we may in this case assume that it has existed in a

latent form for about 20 years, becoming manifest by provocation with stilbestrol.

The second case was that of a 40 year-old woman who had had neither angina nor erythema nodosum. In connection with a sulfathiazole treatment of an impetiginous eczema she developed an erythema nodosum-like eruption on the second day of treatment. A month later I succeeded in provoking a recurrence of her erythema nodosum with stilbestrol. Provided that the patient's assertion of never having taken sulfonamides was true it is difficult to consider her sulfathiazole erythema nodosum as manifestation of a sensitization to sulfathiazole, the lesions having appeared on the 2nd day of the medication.

In both cases it was a question of synthetic estrogen. Consequently it can by no means be taken for granted that the outbreak of erythema nodosum really was provoked by an estrogen hormone factor. The synthetic estrogens, as is well known, provoke side-effects more easily than natural preparations.

Perhaps we have only to do here with a so called "drug eruption", and not with an "idiopathic" erythema nodosum. However, a great many scientists share the opinion that erythema nodosum due to drugs, e.g. sulfathiazole, cannot be strictly separated from erythema nodosum idiopathicum, either clinically or histologically. (*Greither, Keil, Löfgren, Miescher, Tachau* a.o.)

Löfgren says that "the exanthemas arising after the administration of certain types of drugs, which have been described as "toxic erythema nodosum", ought in point of fact to be interpreted as having an infectious origin, and that the medication has only played the part of a provoking agent". Like many other Scandinavian authors he regards erythema nodosum as a non-specific hyperergic condition which may arise in connection with a number of different infections. According to *Bergstrand* it is perhaps a hypersensitivity reaction of the anaphylactic type, and presumably due to the protein or the carbohydrate component in the bacillary body. *Greither* mentions the negative result of the epi-

cutaneous and intracutaneous skin test, the missing eosinophilia, the high sedimentation rate, the histological structure and the total clinical impression reminiscent of an acute infection as factors pointing against a drug allergy.

Accordingly the erythema nodosum-like drug eruptions also would be a question of an infectious process with a possible biotropic activation of hidden micro-organisms (biotropism—*Milian*). The thought of a latent virus infection, made manifest by different provocations in the same way as herpes simplex or herpes zoster, comes to the mind (comp. *Miescher*).

The outbreak of herpes simplex in women coincides in a considerable percentage of cases with the premenstrual phase of the cycle, i.e. synchronomous with high estrogen levels or may be changes in hormonal actions. According to old statistics by *Bergh* in Copenhagen, 644 out of 877 cases of pro genital herpes were of menstrual origin. Erythema nodosum arising premenstrually or provoked by estrogens thus offers close points of contact with herpes menstrualis. The menstrual urticaria, on the other hand, must be interpreted as an allergic manifestation.

Certain other conditions occurring premenstrually, like the premenstrual recurring ecchymoses described by *Stiller*, *Wilhelm*, *Behrend* and others, may also be mentioned in this connection.

The mode of action of the hormones in all these cases is far from clear. Their influence on the vasomotor system with hyperemia and changes in the permeability of capillaries etc. may perhaps be regarded as a contributory factor. Experiments on animals as to the influence of estrogen on bacterial and virus infections have given partly contradictory results. According to *Sprunt* and *McDearman*, *Foley* and *Aycock*, and *von Haam* and *Rosenfeld* estrogen exerts a protective influence against acute infections caused by vaccinia virus, streptococcus and pneumococcus, respectively. *Lurie & al.* have found that estradiol dipropionate retarded the tuberculous process at the site of inoculation in the skin and to

a considerable degree suppressed its dissemination in the body. By contrast, the periodic administration of chorionic gonadotropin, which induced successive crops of corpora lutea in the ovary, uniformly enhanced the tuberculous process at the site of cutaneous inoculation, increased its dissemination, and aggravated the extent of the disease in the internal organs. They found further that estrogen reduced the inflammatory response of the skin to tuberculin in sensitized rabbits by virtue of the depressing effect of the hormone on the inflammatory irritability of the skin to bacterial irritants in general. *Aycock* and *Foley*, on the contrary, have stated enhancement of tuberculous infection in guinea pigs by steroid hormones.

Many interesting problems are still unsolved. Further investigations also into the possible relationship between estrogen and erythema nodosum are desirable.

SUMMARY

A short survey of the literature concerning premenstrual erythema nodosum is given, and the possible connection between sex hormones and erythema nodosum briefly discussed. The case of a 37 year-old woman is described, who on three occasions developed erythema nodosum in connection with stilbestrol treatment (Diethyldioxistilbene dipropionate). In another case, a woman, aged 40, who had recently suffered from erythema nodosum due to sulfathiazole, *Sonck* succeeded in provoking a recurrence with synthetic estrogen. Further investigations into the possible relationship between estrogen and erythema nodosum are desirable.

ZUSAMMENFASSUNG

Das Vorkommen von praemenstruellem Erythema nodosum und der eventuelle Zusammenhang zwischen Geschlechtshormonen und Erythema nodosum ist im Kurzen erörtert. *Sonck* beschreibt den Fall einer 37-jährigen Frau, die im Anschluss an Stilboestrolbehandlung bei drei Gelegenheiten einen Ausbruch von Erythema nodosum bekam. Bei einer

anderen Frau, die kurz vorher an Sulfathiazol-Erythema nodosum gelitten hatte, gelang es *Sonck* mit Stilboestrol ein Rezidiv hervorzurufen. Weitere Forschungen bezüglich dem eventuellen Zusammenhang zwischen oestrogenen Hormonen und Erythema nodosum sind wünschenswert.

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For further references see the monographs of
Löfgren and *Tachau*.

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