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НАУКОВЕ ТОВАРИСТВО ІМ. ШЕВЧЕНКА В ЗДА
302-304 WEST 13TH STREET, NEW YORK 14, N.Y.

PAPERS — ДОПОВІДІ

Ч. № 19

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ROLE OF NON-THYROXINE PROTEIN-BOUND-IODINE IN IDIOPATHIC ERYTHEMA MULTIFORME

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РОЛЯ НЕ-ТИРОКСИНОВОГО, БІЛКОВИНАМИ ЗВ'ЯЗАНОГО ЙОДУ В ІДІОПАТИЧНІЙ ERYTHEMA MULTIFORME

Shevchenko Scientific Society
New York, N. Y.
1961

Поручили для публікації 15. грудня 1961 року

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Ціна $0.70

...*"I cannot see much improvement in this connection until more clinical dermatologists are trained in biochemistry and more biochemists in dermatology... For the biochemist without knowledge of dermatology is myopic but the investigative dermatologist without knowledge of biochemistry is impotent and his endeavours will be unfruitful..."*

A. Tickner: The biochemistry of psoriasis, The British Journal of Dermatology, Volume 73, No. 3, March 1961, P. 87.

ROLE OF NON-THYROXINE PROTEIN-BOUND-IODINE IN IDIOPATHIC ERYTHEMA MULTIFORME

(Preliminary Report)

by

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Under the term idiopathic erythema multiforme, we undertand in accordance with Sauer's classification: 1. Erythema multiforme, as originally described by Hebra. 2. Stevens-Johnson syndrome. 3. Erythema multiforme bullosum. The symptomatic types called by Lewis, multiform erythema group, are not related to the aforesaid conditions.

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Organic (hormonal) iodine in blood serum is usually called protein-bound-iodine, abbreviated PBI, which we shall use hereafter. A great majority of investigators admit that normal limits of serum PBI are from 4.0 to 8.0 gamma per cent.*

Rapport and Curtis, (p. 744) write that... "the exact nature of PBI is unknown"... and that (p. 744)... "its chemical identity is poorly understood." This statement is in full agreement with Salter's opinion that... "qualitative nature of blood iodine compounds... is largely unknown." Serum PBI contains thyroxine. But how much? We do not know exactly as... "no suitable clinical methods exist for estimating actual circulating hormone." (Rapport and Curtis — p. 743).

Peters and Man admit that there is reason to believe, that PBI may be largely, if not chiefly composed of thyroxine. This opinion is in contradiction with the fact (also observed by them) that in profound hypoalbuminemia, PBI level is as low as in myxedema, but the symptoms of hypothyroidism are lacking (Chaney).

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* A gamma (also called a microgram) is 0.001 milligram.

In experiments of Keitel, the administration of testosterone induced marked depression of PBI, but clinical hypothyroidism was not observed. In experiments of Carter and co-workers 17—methyl—19—nortestosterone led to a profound fall in the serum PBI, but increased greatly BMR. According to Dodds, there is no quantitative relationship between the level of PBI and BMR. Perkin and Hurxthal, as well as Silver and Tyson, were unable to demonstrate any correlation between the PBI level and BMR. Goldberg, Wolff, and Greep, conclude that... "it is possible that the level of plasma PBI bears little relation to the actual level of circulating thyroid hormone."

We may quote several additional observations of different authors, to support such an opinion. Dinitrophenol (Wolff, Rubin, and Chaikoff) induces rapid decrease in PBI, but increases BMR from 20 to 30 per cent (Cushny). Chlorpromazine (Reichlin, Koussa and Witt) and diphenylhydantoin (Oppenheimer and co-workers) lower PBI significantly without producing symptoms of hypothyroidism. Starr's patient without symtoms of myxedema presented PBI level of two gamma per cent. Among the children with endemic goiter, but without any symptoms of hypothyroidism, Ramalingaswami and co-workers found four patients with PBI between one and two gamma per cent. According to Ingbar, PBI can fall as low as 0.8 gamma per cent, but the patient my remain clinically asymptomatic.

On the other hand, cretins with congenital absence of thyroid gland will usually present PBI of from 0.5 to 2.0 gamma per cent (Wilkins). This author suggests (p. 76) that in thyroid gland, there may be... "other (unknown) compounds which have a biologic role in health and in disease." By the end of 1956, according to Chaney, at least 17 iodine containing compounds were identified in body fluids and tissues as free or as constituents of at least three proteins.

In 1960, two new types of iodoproteins other than thyroglobulin, synthesized independently from thyroglobulin, were found in thyroid tissue of rats and men by Rall and co-workers. According to Homolsky and Freedberg ..."The physiologic significance of other (than thyroxine) compounds, found in PBI, in small variable amounts remains to be determined."

We should conclude in the last analysis that little is known about the compounds constituting PBI besides the thyroxine; that further fractionation of the PBI into its several compounds, chemical identification of unknown compounds and determination of their significance in health and in disease appears necessary.

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Weiss thinks that erythema multiforme is due to "a vasomotor disturbance of toxic origin"; Cannon that it is a "profound toxemia"; Heller that it is a disease of "toxic nature"; Garnier that it is a condition "due to a hormonal imbalance." Percival writes that ... "the disease is undoubtedly due to internal factors .... the cause is unknown, but the uniformity of clinical picture suggests that a specific toxin is responsible." Ormsby and Montgomery admit that erythema multiforme ... "is due to toxemia of undetermined origin"; Leopold thinks that ... "the causative factor appears to be based on some internal toxic condition"; Elson that erythema multiforme ... "is a disease caused by toxin being generated constantly in the patient."

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Garnier described the case of a 26 year old woman who "repeatedly" developed erythema multiforme at the time of menstruation. In Chargin's case, the patient stated that the attacks of erythema multiforme came on with her menstrual periods. In the case of erythema multiforme perstans described by Williams, the eruption worsened just before and during menstruation. In one of the erythema multiforme cases collected by Forman and Whitwell (case No. 12) the appearance of the disease was provoked by menstrual periods or sunlight, for ten years.

Few interesting erythema multiforme cases, correlated with menstruation, were collected by Bulkley. In the case originally described by Lallier, the patient presented erythema multiforme lesions on the back of her hands with each menstruation for eight months. Another case (originally described by Goutry) was a 34 year old woman who developed erythema multiforme lesions for the first time at the age of 16. The disease recurred with each subsequent menstruation and ceased during pregnancy after her marriage at the age of 21. The attacks of erythema multiforme reappeared with the menses, but were arrested by the next pregnancy. After delivery erythema multiforme started to appear again, either a few days before or at the onset of each menstruation. In the third case, collected by Bulkley (originally described by Stiller) a 30 year old woman with amenorrhea, developed erythema multiforme if there was much delay and the menses did not appear at the proper time. In the case of Leredde, a 33 year old woman presented erythema multiforme lesions with almost every menstruation for nearly twenty years.

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During menstruation the total blood iodine level increases (Veil and Sturm, Maurer, Maurer and Diez, Jahn and Kesselkaul, McCul-

logh, Scheringer (1940), Curtis, Leipert and others.) Salter writes: "In general there seems to be a definite rise in blood iodine at the onset of menstruation, amounting to about 25 or 30 per cent of the normal". In thyrotoxicosis the total blood iodine during menstruation increases even more (51 to 86 per cent of the normal — Jahn and Kesselkaul). Urinary excretion of iodine during menses increases (Cole and Curtis). The menstrual blood may contain from 42 to 113 gamma per cent of iodine (Jahn and Kesselkaul). We have been unable to find any studies about the level of serum PBI in menstruation.

During menstruation physiological swelling of the thyroid may occur (Maurer and Diez). It is presumed that this reflects a normal increase in thyroid activity. According to Benedict and Finn, the oxygen consumption during menstruation lowers. They write that menstruation appears to be ..."a real factor lowering the metabolism." This is in accordance with the results of investigation of Gustafson and Benedict, who also write that the metabolism during the menstrual period is lowered. We conclude that the rise in blood iodine during menstruation is not due to increase in thyroxine.

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Material collected from literature suggests that erythema multiforme may be related to pregnancy. In the case of Crawford and Leeper, erythema multiforme developed one month before delivery. The patient gave a history of previous attacks, unrelated to pregnancy. While discussing this case, Trow reported that he observed a patient with erythema multiforme in two pregnancies, with an attack between pregnancies typically that of erythema iris. In the case of Gross, a 33 year old woman developed erythema multiforme gestationis during two of her pregnancies. Kingsbury's patient developed erythema multiforme lesions during "all" her pregnancies for five years.

At the meeting of the New York Dermatological Society in February, 1927, McKee while discussing the case of Whitehouse reported that he had seen a number of cases of erythema multiforme gestationis. In every instance the disease lasted until the pregnancy was terminated by natural or artificial means.

At the Chicago Dermatological Society meeting in March 1927, Ebert presented a six month pregnant patient with erythema multiforme lesions on her forearms. She developed similar changes also during her previous pregnancy. While discussing this case, Driver reported a patient who developed erythema multiforme during her

three pregnancies. During the last pregnancy the attack was so severe that a therapeutic abortion became necessary.

At the Manhattan Dermatological Society, in December 1909, Gottheil presented a 33 year old pregnant woman who developed erythema multiforme during each of her four pregnancies. Between the pregnancies, she was completely asymptomatic, even when the interval between two pregnancies was as long as four years. The last time the patient became pregnant in August, 1909. Erythema multiforme lesions appeared three weeks later.

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Rapport and Curtis (p. 741) write: ... "during pregnancy ... the the PBI .... rises sharply as early as the third week and remains elevated until delivery, after which it rapidly returns to normal. This rise in blood iodine ... is not accompanied by the other manifestations of hyperthyroidism. Indeed, the serum cholesterol frequently increases, as in hypothyroidism".

According to Chaney ... "during pregnancy there is a demonstrable increase in serum PBI, which is not associated with any symptoms of hyperthyroidism." Ingbar (p. 62) states that ... "during pregnancy there is evidence of thyroid hyperplasia, high PBI, and high radioiodine uptake, the usual features of hyperthyroidism — yet there is no evidence of hypermetabolism at least in the first half of pregnancy."

In pregnancy urinary excretion of iodine increases (Cantarow and Trumper, Enright). According to Scheringer the average daily urinary output of iodine in pregnancy amounts to 311 gamma, while in non-pregnant women, 164 gamma.

According to Seitz, thyroid hyperplasia develops in 70 to 80 per cent of pregnant women. "It is generally agreed — write Rapport and Curtis (p. 741) — that hyperplasia of the thyroid gland is physiological during pregnancy and it has been presumed that this reflects a normal increase in thyroid activity. Many investigators have confirmed an elevation of the total blood iodine and of the PBI associated with gland hyperplasia."

Increase in size of thyroid gland — according to Bokelman and Scheringer — indicates hyperfunction. This hyperfunction, however, is not due to increased thyroxine production, as symptoms of thyrotoxicosis are lacking.

In pregnancy and in erythema multiforme, there is tendency for water retention. In thyrotoxicosis, for dehydration of the tissues. According to Drill .... "administration of thyroxine increases maximal rate of water diuresis."

Robbins and Nelson admit that there is significant lowering of free thyroxine in serum of pregnant women despite the rise of PBI. The increased serum PBI in pregnant women seems to be an estrogen effect. In certain habitual aborters PBI fails to increase during pregnancy. According to Sherer administration of diethylstilbestrol in such cases increases PBI and permits habitual aborters to carry to term uneventfully.

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Thomas writes: "A recognized feature of erythema exudativum multiforme is its tendency to be recurrent." "There is a definite seasonal incidence — writes Tobias — most of the cases occur in spring and fall." According to Pillsbury: "Annual or semi-annual recurrences are not unusual, often in the same months of each year." In the case of Fornbacher, erythema multiforme appeared in spring only, for "few years." Arzt's patient presented lesions of the disease in spring only, during six years, and Lowy's, during nine years. Cuthbertson described a case of erythema multiforme in a 27 year old woman, who, from childhood developed the lesions always in the fall.

In Thomas' case a 27 year old policeman developed "sore mouth" in 1938 and "sore throat" once every year from 1939 to 1942. In 1943 lesions on buccal mucosa were accompanied by cutaneous erythema multiforme lessions. Recurrences similar to the last one, the patient also presented in 1944 and 1945. In Butler's case, a 17 year old boy developed severe erythema multiforme in October, 1918. About one year later he had a similar attack and two subsequent recurrences at five month intervals.

In a case presented at the Philadelphia Dermatological Society in October 1921, by Walker, a 23 year old ship carpenter had six attacks of erythema multiforme, all in the months of May and October. In a case described by Gougerot and Eliascheff, erythema multiforme appeared every six months for four years. In March, 1937, at the Munich Dermatological Society, Vonkennel presented a 32 year old man in whom erythema multiforme developed every six months for seven years. In Ormsby's case a female patient with erythema multiforme had recurrences of the disease twice a year, for nine years.

Hufnagel described a case of erythema multiforme with severe attacks of the disease each spring and fall for ten years. A similar case of the disease recurring once or twice a year for ten consecutive years was presented in March of 1944, at the Manhattan Dermatological Society by Lewis. In case of Weiss, a 50 year old man presented symptoms of erythema multiforme in the spring and autumn yearly for twenty years. In the case of Friedmann and Pathé, a fe-

male patient presented the lesions of the same disease usually in spring, but also occasionally in the fall for twenty-one years.

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The largest statistics of erythema multiforme ever published are those of Ustinowskyj from Moscow (495 cases). They present two clearly defined maxima: the first in May and the second in November (Fig. 1).

Havelock Ellis writes that in Europe the maximum of conceptions occurs in May and June, and then in November and December.

The statistics of conceptions in this country, we found in the Statistical Bulletin of the Metropolitan Life Insurance Company(Vol. 23, No. 8, Page 7) show two clearly defined maxima of conceptions, the first in May and the second in November (Fig. 2).

The statistics of erythema multiforme collected by Jordan, Duhring, Chirghinoff, Zwecker, and Noojin and Callaway, are small and therefore not suitable for more detailed interpretation. They show, in general, also two maxima of cases: in spring and in autumn. Of special interest to us were the statistics of Hausmann and Haxthausen from Copenhagen, Denmark, the second largest published (237 cases), since they are the only statistics known, presenting only one maximum (in June).

Statistical data of births from 1955 to 1957 (three year period) for Denmark, received from the Royal Danish Consulate in San Francisco, California, calculated for the data of conceptions are presented on fig. 3. They show only one maximum of conceptions in June, i. e. in the same month in which also the maximum of erythema multiforme cases occurs.

Statistical data of births, in ten year period (from 1921 to 1930) received from the American Embassy in Copenhagen in confrontation with statistical data of erythema multiforme cases are presented on fig. 4. They also show the maximum of conceptions in the month of June. The material collected is large enough to exclude accidental coincidence.

We conclude that the maximum of erythema multiforme cases appears at the time of the highest number of conceptions.

Danish people are of Nordic origin. They evolved in a harsh environment in which only one sexual season annually was possible in the pre-domesticated era of humanity. (In the temperate zone there were two such seasons). The only maximum of conceptions simultaneous with the only maximum of erythema multiforme cases has a biological background and reflects the only annual sexual sea-

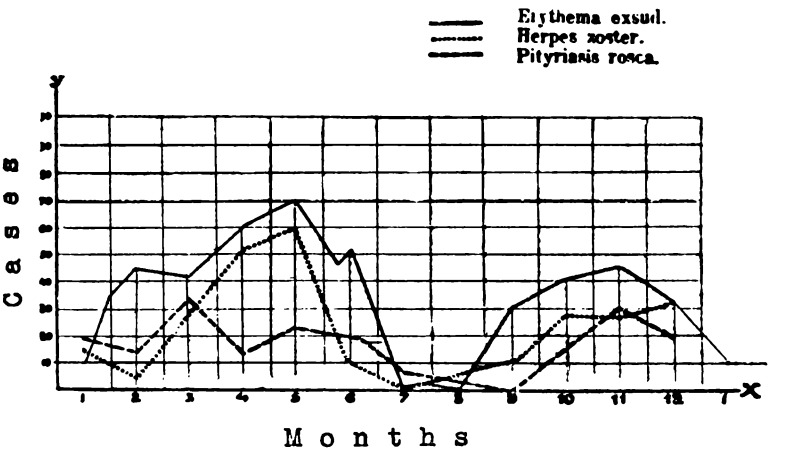

Figure 1.

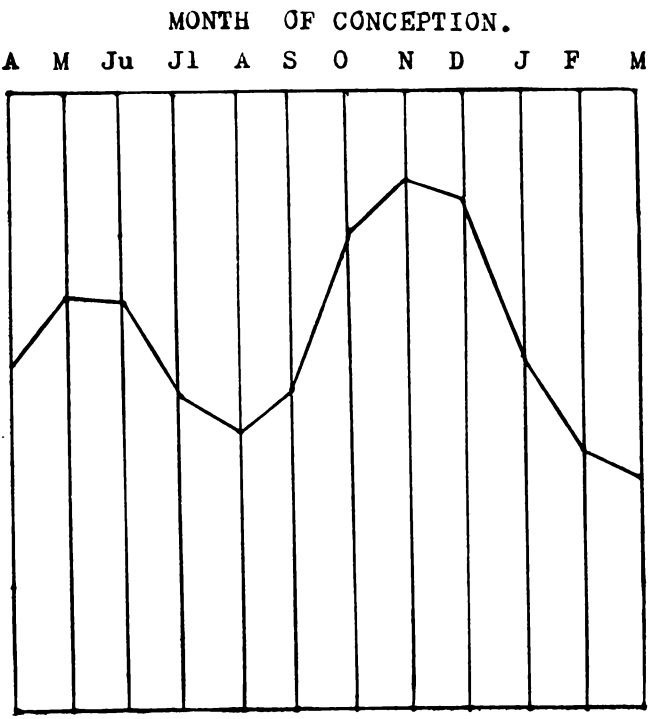

Figure 2.

Curve of conceptions in three year period (1955 thru 1957) and the curve of Erythema Multiforme cases show, in Denmark, only one maximum in the same month (June)

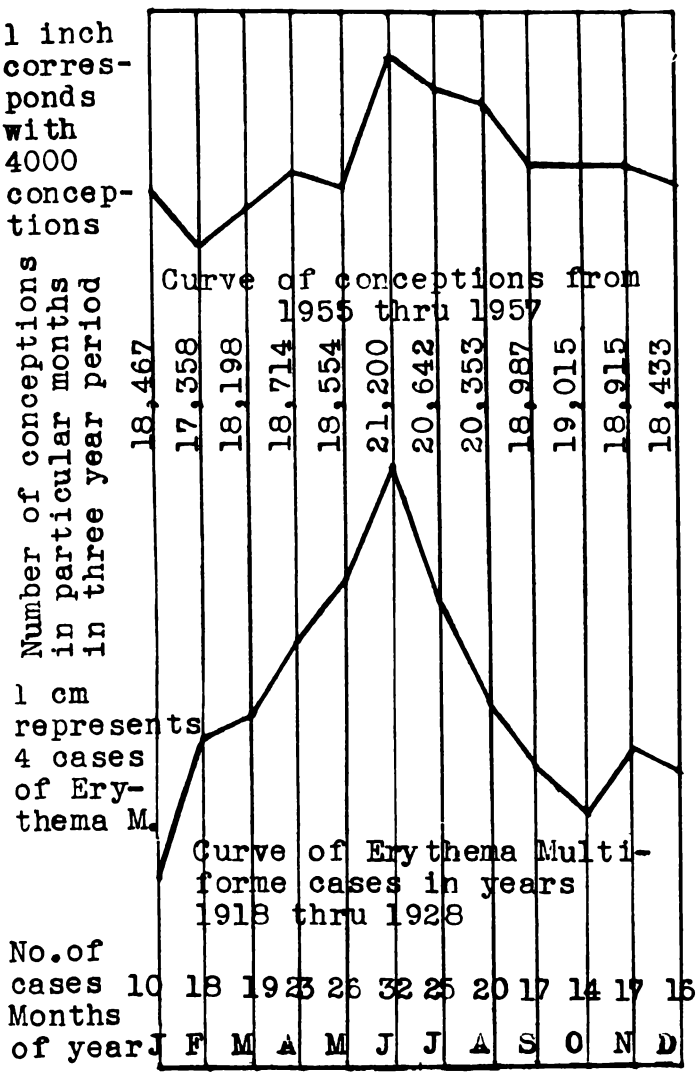

Figure 3.

Curve of conceptions in ten year period (1921 thru 1930) and the curve of Erythema Multiforme cases show, in Denmark, only one maximum in the same month (June)

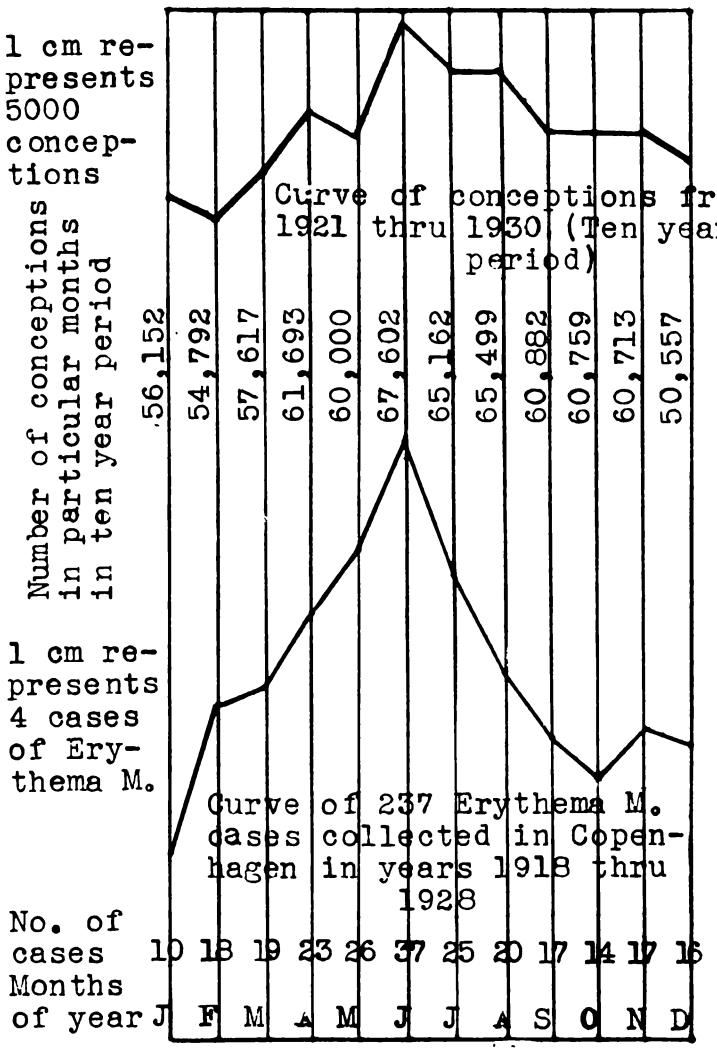

Figure 4.

son the Danish people had in the far distant past. The problem is a very interesting one, but is beyond the scope of this paper.

Material collected from literature indicates that in animal world iodine metabolism during sexual season is disturbed.

In Central Europe iodemia is highest and thyrotoxicosis most frequent in May.

May is called by German authors "Basedow-Monat" (Month of thyrotoxicosis).

The problem will be worked out in details in the near future.

From our point of view it is of special interest that erythema multiforme never develops in castrates. After castration PBI level in animals lowers.

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According to literature, in the treatment of erythema multiforme, cortisone and ACTH are drugs of choice. In studies of Hill and coworkers these drugs lowered PBI in 8 of 13 subjects. This explains why erythema multiforme may or may not respond to administration of cortisone and ACTH. In experiments of Perry, ACTH and cortisone depressed the radioiodine uptake by the rat thyroid. Both the thyroxine and non-thyroxine radioiodine of the gland were lowered.

A few years ago we introduced vitamin D into the treatment of erythema multiforme (50). In our cases the method proved to be a fully reliable one. It was worked out on the base of the experiments of Goormaghtigh and Handowsky who found that the thyroid of the dogs fed with large doses of vitamin D, shows histological picture of depressed activity. It became understood that the large doses of vitamin D depressing the thyroid activity will depress the synthesis of thyroxine in the gland. As the drug in thyrotoxicosis appeared ineffective the paper was disregarded and soon forgotten. Our experiments proved that vitamin D, lowers PBI and cures erythema multiforme.

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We had the opportunity to determine serum PBI level in the disease and in health in four patients with idiopathic erythema multiforme.*

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* Laboratory tests were performed in Long Island Laboratories, Flushing, New York (Joseph M. Chernaik, Director).

Case	Diagnosis	PBI in disease	PBI in health
1.	Erythema multiforme, Hebra-type (during menstruation)	17.1 gamma per cent Lab. No. C-11188 Reported: 11-19-52	5.6 gamma per cent Lab. No. C-11879 Reported: 12-9-52
2.	Erythema multiforme bullosum	9.8 gamma per cent Lab. No. C-11572 Reported: 12-1-52	5.4 gamma per cent Lab. No. C-12337 Reported: 12-22-52
3.	Erythema iris type	5.4 gamma per cent Lab. No. C-21429 Reported: 8-13-53	4.9 gamma per cent Lab. No. C-22583 Reported: 8-28-53
4.	Stevens-Johnson syndrome	7.5 gamma per cent Lab. No. C-67382 Reported: 5-9-56	6.4 gamma per cent Lab. No. C-69903 Reported: 6-21-56

CONCLUSIONS

Idiopathic erythema multiforme is a toxemia, caused by certain unknown organic iodine compound or compounds synthesized independently from the thyroglobulin in the thyroid.

In females this condition seems to be an estrogen effect.

In erythema multiforme, the PBI is much higher in the disease than in health.

Drugs lowering non-thyroxine PBI cure the disease.

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