Prurigo nodularis.

By

Susumu Iijima.

(飯 島 進)

(From the Department of Dermatology, Faculty of Medicine,
Tohoku University. Director: Prof. M. Ito.)

(Received for publication, August 20, 1950)

Recently I observed several cases of prurigo nodularis and obtained some interesting result concerning its etiology, the abstracts of which were already reported in this journal.¹⁾ Here the detailed description of the experiments will be given.

Historical Review.

In the past fifty years this disease was studied by many investigators. Most of them looked upon this either as a variety of urticaria, urticaria perstans, or as a sort of lichenification of Brocq-Pautrier, or as a sort of prurigo, prurigo nodularis. There are some, however, who advocated their own theories and designations.

The oldest conception, the persistence of the wheal was first proposed by Willan and Bateman.²⁾ F. J. Pick³⁾ in 1891 reported five cases under the title of urticaria perstans. But some of his cases belong to urticaria pigmentosa and others to what Kreibich later called urticaria perstans simplex, the existence of which is under discussion. The first case bearing certain resemblance with our disease in German literature was reported by Fabry⁴⁾ in 1896. Kaposi⁵⁾ referred to urticaria verrucosa in his handbook which he regarded as the secondary deformation of the wheal in old individuals. Kreibich,⁶⁾ in his article over urticaria chroica, reported two cases of urticaria perstans verrucosa which quite corresponded with prurigo nodularis. He emphasized the urticarial nature of this disease because of the coexistence of the wheal in his case. Hartmann⁷⁾ reported similar cases under the title "Ueber urticatielle Hauterkrankungen" and refuted the relationship with urticaria and noted that the eruption was the result of primary pruritus. Thus he ascribed this to a sort of prurigo. Hübner⁸⁾ also rejected the urticariogenesis and proposed a new name suggestive of the secondary granulomatous nature, tuberosis cutis pruriginosa, while Fabry⁹⁾ in his later article accepted the coincidence with the lichenification of Brocq and advocated a new name, neurodermitis nodulosa.

Rasch¹⁰⁾ introduced Hyde's designation for the first time in the German literature in 1916. In 1920 Ahrens¹¹⁾ of the Unna's school believed to have found the eczematous origin and proposed another name *eczema verruco-callosum nodulare*. Vohwinkel¹²⁾ recommended the naming *lichen obtusus vulgaris* and rejected the confusion with *urticaria perstans* in Wolter's sense. In 1932, Bohnstedt¹³⁾ added some new findings by ascribing *keratosis verrucosa* of Weidenfeld to the group of *prurigo nodularis*.

In America this disease was more clearly recognized. Hardaway¹⁴⁾ first of all, then Corelet,¹⁵⁾ Johnston,¹⁶⁾ Schamberg-Hirschler¹⁷⁾ reported similar cases without contributing them to no preformed categories except White¹⁸⁾ who accepted the theory of lichenification. In 1909 Hyde¹⁹⁾ gave the name of *prurigo nodularis* which has since been accepted by almost all authorities in America.

In France Brocq and Pautrier²⁰⁾ were the outstanding investigators in this field. In accordance with the theory of lichenification, they first proposed the name *lichen obtusus corneus*, then abnormal lichenification and finally *lichénification circonscrite nodulaire* was proposed. To them it was beyond doubt that the primary cause ^{chronique} was the pruritus and all clinical picture was the result of "grattage". Some investigators, Thibierge, Nicolas and Gate refuted this theory and emphasized that this is a variety of *lichen ruber* chiefly on the basis of clinical findings. In 1934 Pautrier found hyperplasia of nerve fibers in the eruption and thus attracted the attention of investigators on this point.

Case Report and Discussions.

The author collected 33 cases in this clinic, 14 of which were male and 19 were female patients. The age of onset is shown in Table I.

TABLE I.
Age of Onset.

	under 10	11-20	21-30	31-40	over 41
Own Cases	4	11	12	2	4
Cases in Foreign Countries	5	18	26	20	26

The youngest is 5 and the oldest 71. The season of onset is most often in summer, but there is no definite relationship between the onset of the disease and the season. The site of the eruption in most cases is restricted to the extensor surfaces of the extremities, but in 8 either the face or the trunk or both are involved. Itching of the varying grade is

complained by all and in two the pruritus is the first complaint. Remarkable is the fact that in 12 cases insects bites are blamed as an approximate cause. The disturbance of the menstrual cycle is complained in three, and in two the onset ensued pregnancy or partuition. In cases from foreign literatures are 23 men and 70 women. The age of the onset, which is shown in Table I, is most often between 21 and 30 and in the class over 41. This shift to the older age may not be significant if we take into consideration the difference of the distribution of the population according to age.

Symptoms. The essentials of the symptoms is the production of nodules. They are disseminated mostly on the extremities, nut or pea sized, semiglobular elevated, verrucous in appearance and brownish in color. The other parts of the body may be involved, and the lesions in those parts may have rather smooth and shiny surfaces and are small in size. Thus the fundamental lesion is the isolated nodulous eruption, and the difference between the papulous and verrucous variety lies chiefly in the difference of location. The grouping of nodules is observed by several reporters, but if we are to admit that lichenified patches may be produced in the papulous type, as is maintained by Dohi²¹⁾ and Kitamura,²²⁾ we cannot distinguish it from neurodermatitis. Such instances, if any, can never be admitted into the same category as prurigo nodularis which shows no tendency to plaque formation. Lehner²³⁾ refuted the existence of the papulous variety and enlisted it in prurigo vulgaris.

Pathogenesis. The histo-pathological change in this disease lies both in the epidermis and the cutis. In the former mighty hyperkeratosis, acanthosis and elongation of the epidermal process while in the latter much or less bordered cellular infiltration are usually noted. These never coincide with urticaria or transient edema of the dermal layer. The urticariogenesis of Kreibich cannot be justified. The coexistence of the wheal does not represent the relationship with urticaria any more than the prurigo of Hebra which may start as a wheal-like eruption is a variety of urticaria acuta. The transition of the wheal into the nodule was noticed only by Hieleman. From these it is clear that this belongs to quite different category from urticaria, though the naming of urticaria perstans may be preserved as indicating this particular state. The positive dermographia indicates only the vasolability of the patients and gives no clue to the pathogenesis of the individual eruption itself.

The details of the histological changes vary in a wide range according to the authors. This is chiefly due to the difference of the stage and cannot be significant itself. So it is impossible to draw certain conclusion from some or other histological picture alone. On the other hand the neuroma of Pautrier has been regarded as somewhat pathognomonic

by some dermatologists. The nerve change in this disease was first described by Johnston. He found perineural infiltration and suggested that this might be the cause of the intense pruritus. But proliferation or degeneration was not mentioned. Next came Rasch who observed increase of nerve bundles in the infiltrated parts, but further description was lacking. Ullmann found no morphological changes of nerve fibers. Pautrier stained sections with trichrome method of Masson and found neuroma-like hyperplasia of medullated nerve fibers in the reticulated and papillary layer. His findings were acknowledged by Liebner, Jalomy, Bonnevie, Moncorps and Kitamura and rejected by Bronzini. Recently Perez and Maruri²⁴⁾ noticed hyperplasia as well as degeneration of nerve fibers by silver impregnation method and assumed allergic origin of this disease. The author excised more than ten nodules and examined with hematoxyline eosine, van Gieson's, Weigert's and Masson's staining, and in some specimen with Seto's modification of Bielschowsky's silver impregnation method. In several sections thick nerve bundles were found embedded in the infiltrate near the epidermis. Some of them show abnormal windings as is shown in Fig. 1. But in other parts apparent normal nerve bundles were also noticed. In contrast sections obtained from Hebra's Prurigo and neurodermatitis, nerve fibers are occasionally found in the midst of cellular infiltrates, but they are neither so thick nor show abnormal windings. Some of the Pautrier's illustration, however, especially the figure of isolated nerve fibers near the borderline to the epidermis is finely imitated in a section from a case of systematized hard nevus with intense pruritus (Fig. 2). In a section of a nodule apparent normal Meissner's tactile corpuscle is involved. This is an interesting finding concerning the endapparatus for itchy sensation.

From above I conclude that Pautrier's neuroma cannot be a pathognomonic feature. Its existence depends chiefly on the stage of the eruption (especially in fully developed one). It is quite difficult to find the significans of the nerve proliferation. This can be interpreted in two ways....either primary or secondary. Primary proliferation may not be impossible in view of the fact that nerve fiber can develop with the epidermis as in the case of condylomata acuminata. But it is too hypothetical to assume the viral origin of this dermatose. Blastomatous nature is out of question. If it be the secondary proliferation caused by mechanical irritation, it has common etiology with Amputationsneuroma. But it is not always possible to stain the nerve fiber itself in the subepidermal layer even with silver impregnation method, and Pautrier's observation may be only the proliferation of Schwann's sheath. Therefore, more detailed, if possible, serial examination is required to dissolve this problem.

Etiology. In many cases some or other predisposing factors are re-

Fig. 1. Winding nerve bundle in the center of a nodule.
×200. ↑ nerve bundle.

cognizable. Disturbance of the endocrine and genitary function are most commonly reported... such as uterus infantilis (Bohnstedt), dysmenorrhea (Suldberg and others), onset in menopause (Ormsby, Boronsky, Schamberg), in pregnancy (Schönfeld, Vohwinkel), increase of itching during menstruation (Ortynsky, Wise, Fabry), recovery after thyroidectomy (Cole-Driver) etc. Gastrointestinal dysfunction is noticed by Brandt, Epstein, Wile, Lehner and W. Pick. Neuropathia is observed by Lehner, Ketron, Schoff, Pick, Hirsch-Bruck and others. Ortynsky²⁵⁾ found histological changes in sweat glands and concluded the excretion of menotoxine with the sweat as the cause of pruritus. Similar observation had been made by Netherton²⁶⁾ previously. In my cases the disturbance of the intermediate protein metabolism is usually noticed. On the other hand many factors affecting the skin from outside are also blamed. Felden mentioned mechanical trauma, Mitchel referred to eczematous changes. In Barnewitz's case as well as Barber's and Vohwinkel's photosensitivity was noted. But there remain many in which no presumptive causes are detected.

Here the author call attention to a hitherto overlooked point—the

Fig. 2. Nerve fibers near the epidermins. Section from a case of systematized hard nevus.

×200. ↑ nerve fiber.

etiological relationship of this disease with insect bites.

In this country many investigators observed that the eruption often ensued insect bites. Amongst foreign literatures only Pick, Richter, Schoff, Cole-Driver, and Hirsch-Bruck payed attention to this point. In less than one third of my cases sensitivity to insects bites is complained, and most frequently to a sort of the gnat, *Eusimulium equinum* Thnnaeus. This is a tiny insect about 3 mm. in length, frequents in country region in summer time. Its bite gives rise to an extremely itchy wheal-like eruption about 1 cm. in diameter with characteristic central hemorrhage.

Sensitivity tests were made in the following manner. According to the method of Storm van Leeuwen, 1% suspension of the insect in a solution containing 0,4% NaHCO_3 and 0,5% NaCl is prepared. After 24 hours it is filtered and the filtrate is sterilized twice by 56°C for 30 minutes, and diluted beginning from 1:100. In five cases out of seven this diluted extract gave positive reaction by intracutaneous method. In all positive reacting cases sensitivity to this insect was stated, while in the negative cases susceptibility to mosquito bites was stated though mosquito extract

was not tested. The same extract was injected to 19 control patients (mostly cases with nevus pigmentosus and hemangioma). Only two reacted positive. Further trial was made to obtain desensitization in five cases. Starting from 0,1 cc. of 1:100 solution, gradually increasing doses up to 1 cc. were given hypodermally every other day. In four cases relief from itching was procured after several injections and cutaneous eruptions began to vanish gradually. In two cases given more than fifty injections the skin has become entirely clear (of) eruption leaving pigmented and slightly atrophied spots. They are still under observation. In the first case, a 20 years old girl, no recidive has since occurred, in the other, a 22 years old male, the eruption has almost cleared except for occasional appearance of tiny papulo-vesicles.

This extract showed negative Millon's, biuret and xanthoprotein reaction and positive Molisch's and Liebermann's reaction.

These findings indicates that there exists specific sensitivity in patients' skin against this extract. Liebner,²⁷⁾ though the details of the experiment is lacking, assumes the allergic origin of this disease. My experiments reveal the sensitization of the skin through bites from the gnat. Another fact in favor of this hypothesis is flare up phenomena of the eruption after another bite next year in one case and the aggravation of the pruritus by too hasty increase of the dosage. Antihistaminics, however, were without effect on this disease.

Then to what type of allergy does this disease belong? If it be allowed to classify skin allergy into epidermal and dermal allergy, it is proper to enlist this in the latter because of the positive intracutaneous reaction, as in the cases of hypersensitivity to bees or other insects. The problem whether the itching is the first manifestation of the allergic reaction or the eruption precedes the itching is difficult to answer. Anyway the verrucous appearance is chiefly due to the result of intensive scratching and especially to the characteristics of the location. The difference from normal and other types of abnormal lichenification is explained by assuming that the allergic reaction takes place repeatedly at the site of the eruption and that thus the itching is restricted to the individual eruption.

Naturally it is difficult to ascribe all the cases of prurigo nodularis to the sensitivity to insects bites only. For example Miura observed sensitivity to milk in his case. And the role of insects bite must be carefully estimated. I observed an interesting case in this point. In a healthy 26 years old man, who had insect bite on the lower extremities in summer, a solitary nodule developed at the lower end of the leg in autumn which in all detail coincided with prurigo nodularis eruption. Insect reaction was positive. By next spring this eruption had vanished without any therapy. This reveals the existence of an abortive form or prurigo no-

dularis mitis.

Thus I conclude that prurigo nodularis is mostly a sensitivity dermatose in this country. The sensitivity, however, differs in a wide range in individual case. And in cases with irrecoverable predisposing factors the disease may persist throughout the life if not treated radically, while in slight cases it may disappear by itself.

SUMMARY.

1. 33 cases of prurigo nodularis are reported.
2. In the histological study, the existence of Pautrier's neuroma is verified, the significance of which remains still unanswered.
3. In the study of the etiology, sensitization to insect bites is noticed. This is certified by intracutaneous reaction and further with therapeutic results with the extract.
4. The instance of the abortive form is observed.

References.

- 1) Iijima, Tohoku J. Exp. Med., 1949, **51**, 284.
- 2) Willan and Bateman, cited by Pick (3)).
- 3) Pick, F. J., Prager Zeitschr. Heilk., 1881, Bd. II, 417.
- 4) Fabry, Arch. f. Dermat., 1895, **34**, 21.
- 5) Kaposi, Hautkrankheiten, 1899.
- 6) Kreibich, Arch. f. Dermat., 1899, **48**, 163.
- 7) Hartmann, *ibid.*, 1903, **64**, 381.
- 8) Hübner, *ibid.*, 1906, **81**, 291.
- 9) Fabry, *ibid.*, 1916-16, **121**, 241.
- 10) Rasch, *ibid.*, 1916, **123**, 764.
- 11) Ahrens, Dermat. Zeitschr., 1920, **71**, 823.
- 12) Vohwinkel, Arch. f. Dermat., 1928-29, **157**, 505.
- 13) Bohnstedt, *ibid.*, 1932, **165**, 808.
- 14) Hardaway, cited by Netherton (26).
- 15) Corelet, J. Cut. Dis., 1896, **14**, 301.
- 16) Johnston, *ibid.*, 1899, **17**, 49.
- 17) Schamberg and Hirschler, *ibid.*, 1906, **24**, 151.
- 18) White, *ibid.*, 1907, **30**, 654.
- 19) Hyde, cited by Netherton (26).
- 20) Pautrier, Nouvelle Pratique Dermatologique, 1934, Tome VII, 512.
- 21) Dohi, Sh., Hifuka-Hitsunyokika Zasshi (Jap. J. Dermat. and Urol.), 1920, **21**, 693.
- 22) Kitamura, Rinsho Hifu-Hitsunyokika (J. Cli. Dermat. and Urol.), 1947, **1**, 127.
- 23) Lehner, Zbl. Haut- u. Geschl. Krankh., 1926, **18**, 561.
- 24) Perez and Maruri, Ann. de Dermat., 1949, **10**, 623.
- 25) Ortynsky, *ibid.*, 1937, **56**, 308.
- 26) Netherton, Arch. of Dermat., 1923, **8**, 193.
- 27) Liebner, Zbl. Haut- u. Geschl. Krankh., 1929, **30**, 693.