and required in all 63 blood transfusions to control haemorrhage (Schiller, Neligan, and Budtz-Olsen, 1948). It is possible that surgery is safer in this type of haemophilia than in the type with prolonged coagulation time, but, even so, the risk of haemorrhage is formidable.

Epistaxis and easy bruising were practically invariable. The latter symptom is uncommon in normal males, and more than one intelligent mother in a haemophilic family had diagnosed haemophilia in her infant son on this symptom alone. If the trauma was severe enormous bruises might be produced.

Haemarthroses were infrequent, and this fact provided a very striking difference between this syndrome and that of haemophilia with prolonged coagulation time. If they did occur they were only rarely apparently spontaneous and usually followed severe injury. Frequently only one joint was involved, and the swellings might last for only a week or two and leave slight deformities. As a result most of the adults were not incapacitated by ankylosed joints and were thus able to follow relatively normal lives.

Inheritance.—In the six families, in which there was a familial history this closely resembled the classical inheritance of haemophilia, there being only two apparent discrepancies (family 6, III 9; family 8, I 3). Both these patients were alleged to be normal.

The various members and generations of the same families all seemed to have the same type of clinical picture and degree of laboratory abnormality. The syndrome thus appeared to breed true.

The importance of the recognition that haemophilia can occur with a normal coagulation time cannot be overstressed. Many of these patients had been told that surgery could safely be undertaken, and it was only after alarming haemorrhage had occurred that it was realized that the advice given had been incorrect. These patients must be regarded as haemophiliacs with all the serious implications of that diagnosis.

There are only very scanty references to this syndrome in the literature. The references to haemophilia with normal coagulation time cited earlier also mention a milder syndrome of haemophilia (Birch, 1937; Quick, 1949; Tocantins, 1949). Fowler (1949) stated that some cases of haemophilia are mild, while Sköld (1944) described some cases of haemophilia with normal coagulation time and without haemarthroses. Some of his cases had a normal coagulation time and a mild syndrome, while others in the same family had a prolonged coagulation time and a more severe syndrome. The only extensive papers on this syndrome are those of Davenport (1930) and Haldane (1935), both of which discuss some haemophilic families in whom the clinical picture appeared to be mild. Unfortunately laboratory data are too scanty to be of value.

Summary

The pathology of haemophilia is reviewed. It is pointed out that the disease occurs in varying grades of severity as estimated both clinically and in the laboratory.

Cases occurring in eight families are described in detail because, as part of a larger survey, they were all found to have normal coagulation times, and the other commonly practised blood tests were also normal in the majority of instances. The bloods of these patients were poor at shortening the calcium time and correcting the prothrombin-consumption-defect of known haemophilic blood, however, and clinically there was no doubt whatsoever that these people had haemophilia.

Attention is drawn to the danger of relying on the common bleeding and clotting tests to exclude the possibility of haemophilia.

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THE MYRMECIA

A STUDY OF INCLUSION BODIES IN WARTS

BY

ALAN LYELL, M.D.

AND

J. A. R. MILES, M.D.

(From the Skin Department and Department of Pathology, University of Cambridge)

[WITH SPECIAL PLATE]

The infective nature of warts was first convincingly demonstrated by Jadassohn (1896), who had 33 positive inoculations out of 86 attempted. Ciuffo (1907) found that the infectious agent present in ground wart tissue would pass Berkefeld N, and Serra (1908), Wile and Kingery (1919), and Kingery (1921) Berkefeld W filters. Passage of experimentally produced warts to the second generation was achieved by Tuccio and Coppolino (1912), Kingery (1921), and Ullmann (1923-4). The elementary bodies of human wart virus have never been described, and the evidence for the viral aetiology of warts rests upon the above experiments.

Histological Appearances

On the assumption that warts were due to a virus we looked for inclusion bodies in sections of warts taken from a pilot series of 10 cases. The wart tissue was curetted under local analgesia, and was fixed in formol-Zenker and stained with haematoxylin and eosin. We found that five of the patient's warts contained eosinophilic intranuclear and intracytoplasmic bodies in the prickle-cell layer (Plate, Fig. 1), and in the belief that these were inclusion bodies we named these warts type I, for "inclusion." Warts from the remaining five

patients were devoid of these eosinophilic bodies, and such warts we named type B, for "banal," on account of their commonplace histology.

The most obvious change in the type I wart when seen under the low-power microscope was a gross disorder of the architecture of the prickle-cell layer. The bodies which we found in type I warts were eosinophilic. Those bodies which were intracytoplasmic could be found in the whole depth of the prickle-cell layer. In the cytoplasm of the deepest layer of prickle cells, and also in an occasional basal cell, we could detect minute pink granules (Fig. 2), which in the succeeding layers of cells increased in size and number. Clear spaces soon appeared within the bodies (Fig. 3) and resulted in rings and sickles and other bizarre shapes. The bodies looked as though they were made of red paraffin wax, and this impression was heightened by their apparent fusion in the upper parts of the prickle-cell layer, where they formed large eosinophilic masses surrounding the nucleus (Fig. 6).

As in molluscum contagiosum, not all the prickle cells were involved in the process, and those cells which escaped were compressed between those which were involved. Those deep prickle cells which were affected differed from those which escaped only in the possession of the minute eosinophilic intracytoplasmic bodies, and in particular the prickles of the affected cells were intact. But in the middle layers of the stratum spinosum the affected cells were much swollen, and their nuclei were large and pale. In the nuclei of some of the affected cells there developed intranuclear eosinophilic inclusion bodies which were perfectly round, and which were bordered by a pale halo (Fig. 4). Such inclusions correspond with intranuclear inclusions type B of Cowdry (1934): these type B inclusions must not be confused with the type B warts of this paper.

At the level of the stratum granulosum the intracytoplasmic inclusion bodies became fewer and larger, and clothed the nucleus. The nuclear substance changed, first from a translucent to a ground-glass appearance (Figs. 4-6), and then became basophilic. The intranuclear inclusions disappeared at this level.

In the stratum corneum the nuclei of the affected cells persisted for a time, became deeply basophilic (Fig. 7), and then shrank and split or fragmented (Fig. 8), until finally they and the fused masses of the intracytoplasmic inclusions became extensively vacuolated (Figs. 9 and 10).

The whole substance of the wart was not uniformly involved by the process; the central part was more affected than the peripheral, and portions of individual papillae were spared. The unaffected parts of the stratum spinosum were seen to underlie those areas of the horny layer which were devoid of nuclei.

There is a close similarity between the histology of molluscum contagiosum and that of type I warts. In molluscum contagiosum there is the same involvement of some of the prickle cells, and the altered cells can be traced from the bottom of the prickle-cell or even the basal-cell layer. The development of the inclusion (molluscum) bodies can be followed through the successive epidermal layers; between the affected cells can be seen the squeezed remnants of those which have escaped. There are two main differences between the diseases: in molluscum contagiosum the nuclei of the affected cells are displaced by the developing inclusion bodies, whereas in type I warts the nuclei remain central, and

there are no wart bodies produced comparable to the molluscum bodies.

The staining reactions of the bodies in type I warts are those which would be expected of inclusion bodies. Thus they stain with Mann's, Laidlaw's, and Downie's stains, but not by the Feulgen technique or by the Prussian-blue reaction for iron. With Feulgen's stain the intranuclear inclusion bodies show up as pale areas within the nuclei in contrast with the nucleoli, which are dark. We were unsuccessful with the phloxine-tartrazine stain, but Lendrum (1947) illustrates a type I wart in his paper on this stain.

Clinical Appearances

After establishing the existence in warts of bodies compatible with inclusions we examined a larger series of cases. The warts from 102 consecutive patients were examined microscopically with the same method of fixation and staining as before. Their warts were type B in 62 cases, type I in 36, and of an intermediate type in 3. The remaining patient had a lesion which was histologically a granuloma pyogenicum, and he was excluded.

The type I warts were mostly plantar, palmar, sub-ungual, or on the pulp of a digit, whereas the type B warts were predominantly common warts of the fingers, face, scalp, and knees. A clinical diagnosis of the expected histological type was eventually possible and, apart from the site of the warts, depended on the following features. Pain, redness, and swelling were commonly associated with type I warts, and in some cases had led to the diagnosis of a whitlow; no pus was found macroscopically or microscopically. Symptoms and signs of inflammation in type B warts were invariably associated with obvious pus formation.

The type I warts were deeply set in the skin, and could be compared to an iceberg floating in water, in contrast with type B warts, which were set superficially, like a cork floating on the surface. As a result the type I warts looked like little molehills with domed tops, while the type B ones were typical warty excrescences. Type I warts might be completely covered by the horny layer, especially on the soles of the feet, but as a rule the horny layer was incomplete over their crowns and formed a thick hyperkeratotic collar; until this collar was removed the full extent of the underlying wart tissue could not be appreciated. Consequently type I warts lay in a flask-shaped cavity, wider at the bottom than the top, while type B warts lay in a saucer-shaped depression.

Type I warts were single individuals, and their cavities were therefore circular in outline. When more than one type I wart inhabited a piece of skin the cavities remained distinct, and there was never the aggregation of many warts into a plaque which was sometimes seen in type B warts: removal of such a plaque would leave a cavity with a polycyclic border. After curettage the type I warts were bulkier than type B, and softer and more resilient to feel; their white opaque bodies and yellowish somewhat friable crowns were of approximately equal thickness, as compared with the tough, horny crowns of type B warts, which were much thicker than and often overshadowed their compact bodies.

The impression conveyed by curetting a type I wart was of plunging the curette into a hole and scraping until suddenly the soft white wart tissue exuded, often in fasciculi like a shallot; type B warts simply needed to be scraped off the skin. The seedlings surrounding type I

warts were set in the skin like sago grains, for the horny layer covered them completely; those surrounding type B warts were on the skin, for the horny layer was interrupted by their presence, and therefore they had a rough surface.

The series revealed other clinical differences. Thus type I warts had usually been present for less than a year (89% of cases), and type B warts for more than a year (71% of cases). Type I cases rarely bore more than five warts (6% of cases), but type B cases often did so (44% of cases). Type I warts responded better to treatment by curettage and cautery (73% clear) than did type B (36% clear) after a follow-up that varied from eight months to two years. The source of infection was presumed oftener in type I (50% of cases) than in type B warts (18% of cases).

Relationship between Type I and Type B Warts

No case was found in which both types of wart were present simultaneously, and this, together with the clinical distinction which we were able to make between the types, convinced us that the histological change which we have called type I was not a freak finding.

We were unable to define the relationship between the two types of wart. Some facts suggested that type B and type I warts were stages of the same process, and others that the types were entirely distinct entities.

Evidence in favour of the unity of the types was that two of the type I cases which recurred produced type B warts; that three of the series had warts of an intermediate type (Fig. 11) in the sense that foci of intracytoplasmic inclusion bodies occurred in what was otherwise a type B wart; that there were some anomalous cases in which there was a conflict between the clinical and histological appearances, though these cases were few and might be explained by an exchange of labels in the section-cutting department; and that, so far as the series allowed us to judge, the types were equally distributed among the Cambridge schools.

In favour of regarding type B and type I warts as distinct entities was a transmission experiment in which 11 volunteers were scarified with a living wart tissue extract. Six received type I and five type B extract, and all had a control scarification with an extract of normal skin. The controls were negative in every case. Of the five who received the type B extract, three produced warts which were clinically type B; the incubation period was 10 to 12 months. All three warts were puny, and for this reason only one could be verified histologically. Of the six who received the type I extract

only one grew a wart. The incubation period was 5½ months, and the wart (Fig. A) waxed fat; after two weeks' growth it was 1.2 cm. in diameter, and alarmed its possessor so much that we were constrained to remove it at once. This wart was type I histologically.

A parallel clinical observation concerned an elderly woman who developed

a type I wart on her index finger: the probable source of this wart was her daughter's verruca, also type I. The mother perhaps contracted the wart by darning and washing her daughter's stockings.

Attempts to distinguish by means of skin tests the type of wart from which a given patient was suffering were unsuccessful. The test extracts were formolized, as was the control extract of normal skin, and each patient was tested against type B and type I warts and the control. The type I extract gave reactions in many cases which bore type B warts, in which the type B extract often produced no reaction.

We had hoped that tryptic digestion might free the inclusion bodies from the epidermal cells, as it does in fowlpox (Woodruff and Goodpasture, 1929), but, although we found spherical refractile bodies 3–10 μ in diameter in the digest, they were produced from both types of wart. Dark-ground and electron microscopy failed to demonstrate free elementary bodies in the digest.

Discussion

We have no doubt that type I warts are a clinical and histological entity. Their clinical features are those of the myrmecia of Celsus—a name which means “ant-hill” and describes their domed shape—of the vascular excrescences of Durlacher (1845), and of the plantar warts of Dubreuilh (1895). Celsus (c. A.D. 25) said that the roots of these warts were deeply fixed, that they were broad underneath, and that they left a deep cavity after removal. Durlacher commented on the pain and throbbing which they occasioned, and the inflammation and swelling which surrounded them. Dubreuilh described the consistency of the wart substance when felt by the curette as “like wet tow.” He mentioned the horny collar which surrounds the warts, and stated that the horn might extend right over the wart and form a roof. Dubreuilh and Celsus recognized that such warts could occur on the palms as well as the soles; we have found that type I warts are commonest on these sites, but also occur beside and under the nails, on the pulp of the digits, and in one case on the face and scalp. Type I plantar warts have room to expand in the thick epidermis of the soles, and in addition are trodden down, hence they are flush with the surface; but on other sites their bulk raises the surrounding skin into the typical dome-shaped lesions which are the origin of the name “myrmecia.”

Not all plantar warts were type I, and among those which were not we found that rarer group which are named “mosaic warts” (Montgomery and Montgomery, 1937). This kind is characterized by aggregations of minute warts with polygonal outlines, roughened surfaces, and superficial growth, which are painless and notably resistant to treatment—all features of type B warts.

From the histological side various observers have interpreted the inclusion bodies as a “keratohyalinoid” degeneration. Dubreuilh (1895) described the intracytoplasmic bodies, and Bowen (1907) the intranuclear ones in addition. The first illustration appeared in Martinotti's (1923) paper and showed both intracytoplasmic and intranuclear bodies, though only the former were described in the text. Percival *et al.* (1947) illustrated the bodies, but regarded them as a degeneration preceding involution of the warts. Meirowsky *et al.* (1948) discussed the bodies as inclusions, but their account was

FIG. A.—Experimental wart, about half actual size.

confused by the introduction of the process of "Hornmarkbildung" into the argument. We believe that the process of "Hornmarkbildung" is quite distinct from the inclusion bodies of type I warts, and occurs in both type I and type B warts. The process is concerned with cornification at the tips of the warts' papillae, and is therefore most in evidence in the filiform and digitate warts of the face—the fibrokeratomata of Unna (1880). The essential difference between "Hornmarkbildung" and type I warts is that in the former the nucleus is displaced to one side of the cell, and in the latter remains central. Whatever may be the significance of "Hornmarkbildung," the process is quite distinct from the type I change.

The bodies in type I warts certainly show staining similarities to keratohyalin; but we believe that they are inclusion bodies because they appear constantly in the deepest prickle cells as well as in an occasional basal cell; because not all the epidermal cells are affected; because in the affected cells we can trace a progressive change through the layers of the epidermis; and because the bodies give the staining reactions which would be expected of inclusions, and do not give those which would not be expected. We have been impressed with the resemblance of the histology of type I warts to that of molluscum contagiosum, a resemblance which fails only in that no wart bodies are eventually expelled from the surface of the wart as are the molluscum bodies. The staining reactions of the wart inclusion bodies and of the keratohyalin produced by the unaffected epidermal cells are not identical, for the inclusion bodies are more eosinophilic, and this difference is not explicable simply because of the larger size of the inclusions.

Inclusion bodies in warts have been described by Lipschütz (1924). They were said to be intranuclear and basophilic, and we believe that they correspond with the inclusion bodies which we have described—for example, Fig. 8; we have emphasized the changes in the subgranular layers of the epidermis, and Lipschütz those in the supragranular layers. He did mention the "keratohyalinoid" change, however, and considered that it bore no relation to the inclusion bodies which he was describing. But we have found that the Lipschütz inclusion bodies are confined to the type I warts.

The intermediate type of warts is uncommon. We have found them in association with type B, but never with type I warts. Dubreuilh described one patient whose warts showed a complete transition from the banal to the inclusion type of histology. We have not found a single patient who has borne type B and type I warts simultaneously.

Finally, we would prefer to drop the names type B and type I warts; this nomenclature was convenient at the time, but was intended only to be a makeshift. In the light of the clinical findings we consider that the type B wart should remain as "verruca vulgaris," while the type I wart should be dignified with its old name, "myrmecia."

Summary and Conclusions

We have found inclusion bodies in some warts: such we have called type I (inclusion) warts, in order to distinguish them from type B (banal) warts, which have a commonplace histology devoid of inclusions.

The inclusion bodies are eosinophilic and are both intracytoplasmic and intranuclear; they appear first in the lowest layer of prickle cells, and their development can be followed into the stratum corneum. The bodies stain as inclusion bodies would be expected to do.

The distinction between type B and type I warts is clinical as well as histological. Type I warts are usually plantar, palmar, subungual, or paronychia; they are painful and often associated with "inflammation" of the surrounding skin; they are deeply set in the skin and form dome-shaped swellings; when curetted their size is greater than appears on the surface, and their substance is opaque, white, and soft.

We are uncertain of the relationship existing between the two types, but some evidence—the recurrence of some type I warts as type B, and the discovery of an intermediate type—suggest that type I warts are a variety of type B. However, other evidence—a transmission experiment and a clinical case in which the warts bred true—points towards an absolute distinction between the types.

The type I wart is the same entity as the myrmecia of Celsus, the vascular excrescence of Durlacher, and the plantar wart of Dubreuilh. Those plantar warts called the mosaic type are histologically type B.

The type I change is quite distinct from the process known as "Hornmarkbildung."

The basophilic intranuclear inclusion bodies of Lipschütz are the supragranular stage of the inclusion bodies of type I warts.

We suggest that the name "verruca vulgaris" be confined to type B warts, and that type I be renamed "myrmecia."

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ADDENDUM.—Since submitting this paper we have seen two reports by Strauss *et al.* (1949, 1950). These authors centrifuged ground wart tissue and found small elementary bodies in type I warts, but none in type B. We are now attempting to repeat this observation.

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FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 1.—Wart, type I. ($\times 90$.) b=Basal-cell layer. i=Inclusion bodies.

FIGS. 2-10.—Wart, type I. ($\times 900$.) Development of inclusion bodies in successive epidermal layers. a=Intracytoplasmic inclusions. b=Nuclei of affected cells. c=Intranuclear inclusions (Cowdry, type B). Eosinophilic structures appear dark in the photographs. Sections at the level of the lower prickle cells (Fig. 2), middle prickle cells (Figs. 3 and 4), upper prickle cells (Fig. 5), granular layer (Fig. 6), and horny layer (Figs. 7-10).

FIG. 11.—Wart, intermediate type. ($\times 90$.) i=Inclusion bodies, in clumps.

FIG. 11