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PART I.

ORIGINAL COMMUNICATIONS.

ART. I.—*A Case of Generalised Vaccinia, with Remarks on the Pathology of the Disease.*^a By RALPH S. OLDHAM, M.D., Univ. Dub.

UNTOWARD symptoms following on, and apparently directly attributable to, vaccination are so uncommon that the following case may be worthy of interest.

A healthy female child, born on Feb. 16, 1907, was vaccinated on March 9, 1907, with the contents of a single glass capillary tube of glycerinated calf lymph obtained fresh from a well-known and reliable firm. At the time of the operation the child's health left nothing to be desired; the skin was smooth and delicate, without any sudamina, and the digestive organs were carrying out their functions perfectly. The skin of the arm was cleansed with a mild antiseptic wash, and the vaccine inserted in four places by scarification with an ordinary blunt sewing-needle, previously sterilised by passage through a flame. The insertions were so placed that rather more than an inch of clear uneroded skin intervened between them; in no case did they exude anything more than a slightly blood-tinged serum, and the vaccine was allowed to dry in before a dry sterilised sponge was sewn lightly round the arm. Directions were given as to the importance

^aRead before the Fylde Medical Society on Tuesday, January 28, 1908.

of keeping the insertions uninjured, clean, and dry ; a powder of oxide of zinc and starch being employed for the latter purpose.

Inspection on the fifth day revealed no symptom that could give rise to unfavourable comment. The site of each insertion was represented by a translucent vesicular multi-loculated plaque invested by a faint zonular blush, to all appearances typical of a normal progress. On the seventh day one or two supernumerary pocks had made their appearance in immediate relation to the two upper original insertions, round which the areola was somewhat more intense and extensive. It was not until the ninth day that anomalous signs really began to manifest themselves, and then the appearance had markedly changed from that of two days earlier. The secondary pocks had enormously increased in number and become correspondingly agglomerated ; those of earliest appearance were transformed into vesicles containing a translucent serum ; many of them exhibited umbilication, whilst others were rounded, plump and tense. The four points of inoculation had reached the pustular stage ; they were enlarged, somewhat flattened, and covered with a dark brown scab. The areola was extensive.

On the following day (the tenth) the accessory pocks round the insertions were innumerable, and mostly confluent. Transformation into pustules had occurred in the vesicles of greatest age, the formerly translucent contents of others had assumed a lactescent appearance, whilst others again—more peripherally situated and of more recent growth—were still clear and discrete, or only semi-confluent. The total area now covered by this confluent mass of pocks was roughly oblong in shape, and measured about 3×4 inches. The arm showed considerable tumefaction, and the areola reached from the shoulder to the elbow-joint. The axillary glands were enlarged and easily palpable. A well-formed vesicle, about the size of a pea, was found on the posterior aspect of the left heel, and another—smaller—one on the left buttock, about an inch from the anal margin.

The next day one vesicle accompanied by two satellite papules, had appeared on the extensor aspect of the left forearm, two on the wrist, and one on the dorsum of the hand. A small papule was to be felt rather than seen on the right buttock, in a position exactly corresponding to that of the vesicle on the opposite side, and obviously produced by contact inoculation. It developed rapidly into a vesicle, and during the next four days pocks

appeared on the ankles, right wrist, left instep, over the right tibia, on the back of the neck, on the occiput, and on the margin of the left nostril. Excluding the left arm above the elbow, the number of isolated pocks totalled twenty-one. The pock mentioned as occurring on the left heel was the first to appear and reached the largest size—viz., that of a threepenny piece. Though not noticed till March 19, probably a more correct date would be the previous day—*i.e.*, the ninth day after vaccination. The remaining pocks appeared successively up to March 23—a period of six days—with the result that the lesions could be viewed simultaneously at all stages of their development; and a description of the progressive stages of any one of them may be regarded as applicable to the others. Appearing first as a light reddish, firm, somewhat conical papule, with a distinctly “shot-like” feeling, it was rapidly transformed into a translucent, well-distended vesicle, sometimes umbilicated, and surrounded by an areola; in the course of a few hours it assumed an opalescent character, turning finally into a shrunken pustule, which was converted into a yellowish scab formed by desiccation of the entire envelope and its contents without rupture. At the same time it must be mentioned that some of the lesions underwent a much more rapid involution than others, while abortion occurred in those appearing on the neck, occiput, and ala nasi, before they had advanced from the papular stage.

The eruptive and inflammatory manifestations in the vaccinated arm reached their acme on March 23, when the appearance was sufficiently alarming (Fig. I.). The areola had now invaded the upper third of the forearm and the anterior and lateral aspects of the chest, downwards to the fifth rib, inwards to the parasternal line, and backwards to the posterior axillary line. The whole of this extensive area was covered by a dense brawny and deeply reddened integument, which, however, at no time bore any resemblance to an erysipelatous rash. The glands in the axilla were swollen, tense, and hard; so much so that it seemed as if their subsidence without suppuration was no longer to be hoped for. The four original insertions were each about the size of a sixpence, depressed below the general surface, even when allowance was made for the tumefaction, and covered by a very black, gangrenous-looking incrustation. Many of the surrounding pustules had ruptured and given rise to a puriform discharge, while the rest were converted into a general greenish-grey crust

(about $4\frac{1}{2} \times 3\frac{1}{2}$ inches), and surrounded by numerous confluent pustules. From this climax of development a retrogressive process set in, at first gradual, but rapidly augmenting, so that within ten days of the turning point of the disease I was able to note:—"The whole arm has cleared up, except for the original insertions, which remain as shallow ulcers, with a healthy granulating floor, exuding a slight sanious discharge. The pocks on the body are either scabbed or completely separated." On April 18 healing was complete.

The patient was suckled throughout, although feeding had necessarily to be restricted to one breast—the left—since the right nipple was slightly cracked. The crack was painted with tr. benzoin. co., and both mother and nurse were warned of the contagious nature of the pocks, and great care was exercised in dressing the arm not to carry infection to the breast. On the evening of April 1 the mother was seized with acute pain in the left breast, radiating from the nipple towards the axilla. She passed a sleepless night, walking up and down the room, and supporting the breast in her hands, as this seemed to afford a small measure of relief. Although I had every reason to admire her fortitude and self-control, she described the pain to be so distracting that she would willingly have submitted to removal of the breast. And, indeed, when I saw her next morning, she looked worn out and wretched enough, with an anxious, sallow countenance, rapid pulse, and a temperature of 102.2° F. Examination of the breast revealed a small fissure at the base of the nipple; extending from this was an irregular ill-defined patch of inflammation passing upwards into the outer and upper quadrant of the mamma; the axillary glands were enlarged and painful. In fact, here were all the evidences of an interstitial mastitis. Nursing was at once prohibited, the breast supported with a firm bandage, and hot fomentations applied to the inflamed area. Considering that this form of mastitis usually goes on to suppuration, it was a great relief on the following day to see a small vesicle in the region of the cracked nipple. Rapidly assuming the characters of a typical vaccine vesicle, it reached the stage of pustule on April 5, and that of scab on the 9th. The pain continued for a week to be very acute, requiring morphin for its relief, but beyond this no other symptoms occurred.

From onset to termination the mildness of the general

symptoms manifested by the infant was truly remarkable. She was restless and irritable, but not markedly so, and certainly not more so than many children in whom vaccination follows a normal course. Her sleep was disturbed to a certain extent, and yet a spell of five hours at night was the rule rather than the exception. The appetite was slightly impaired, and there were for a short time indications of a mild attack of diarrhoea: both of these symptoms, however, might easily have been attributable to the occurrence of a mycotic stomatitis, with which the child was affected at this time; for it was noticeable that the intestinal catarrh ceased as soon as the mouth had been restored to a cleanly condition, a result that was achieved in two or three days by the ordinary therapeutic measures. Any movement of the arm for the purposes of examination, or dressing, naturally gave rise to pain; and yet, in spite of all the Galenical signs of inflammation being so abundantly present, the temperature, taken in the femoro-genital sulcus, never once rose above 99° F., which may be regarded as being within the normal limits for a child of this age (Holt).

The treatment adopted throughout was of the simplest description. As long as the pocks remained unruptured the only indication was to be scrupulously exact in avoiding all extraneous sources of irritation, and to keep them thoroughly dry by a liberal use of the oxide of zinc powder. As soon, however, as they began to discharge their puriform contents the dry dressing was discontinued, and replaced by warm boric fomentations, kept perpetually moist and repeatedly changed. This moist application was substituted for the dry one with the four-fold object of (*a*) absorbing this discharge and preventing any further incrustation; (*b*) of hastening the separation of crusts already formed; (*c*) of lessening the tumefaction and limiting the extension of the inflammatory areola; and (*d*) in the hope of diminishing subsequent pitting, both by facilitating decrustation and by excluding the light. And certainly the improvement inaugurated by this mode of treatment was most gratifying. In twenty-four hours the areola was much less extensive, and not nearly so angry-looking

the swollen axillary glands underwent rapid resolution, the discharge had practically ceased in three days, and eventually the whole scab separated, leaving the subjacent skin only slightly reddened and faintly pitted.

“Such a case opens out the whole question of vaccinal immunity.” So says Acland in referring to a case of his own, which, though apparently due to auto-inoculation, has many points of resemblance to that now under consideration. In order to further accentuate the parallelisms between the two I append a chronological summary of events in imitation of the one set forth by Acland:—

First week (9th March, 1907).—Vaccination with glycerinated calf lymph.

First week (14th March, 1907).—Inspection. Four healthy vesicles, to all appearance normal.

Second week (16th March, 1907).—One or two supernumerary pocks present.

Second week (18th March, 1907).—The four pocks enlarged and covered with dark brown scab. A great number of secondary pocks, at first vesicular, found round points of inoculation.

Second week (19th March, 1907).—Innumerable secondary pocks round insertions, some vesicular, others pustular, forming a confluent mass. Areola extensive. A large pock appeared on back of heel, another on buttock.

Second week (20th March, 1907).—Pocks on forearm, wrist, and right buttock. (Pocks appeared on ankles, wrists, instep, back of neck, occiput, and ala nasi.)

Third week (23rd March, 1907).—Arm very red and brawny, glands in axilla much swollen. Points of insertion very black, depressed and gangrenous-looking, in the midst of a general greenish-grey scab, which discharged a puriform fluid. Pustules on the outskirts confluent. Moist boric lint applied to arm.

Third week (24th March, 1907).—Areola much less; discharge still continues. Pocks on body umbilicated and shrunken.

Third week (26th March, 1907).—Discharge greatly lessened. Involution of other pocks continuing normally.

Fourth week (30th March, 1907).—Condition much improved.

Fourth week (1st April, 1907).—Whole arm cleared up except for original insertions, which remain as healthy ulcers. Pocks on body scabbed or separated.

Fourth week (2nd April, 1907).—Mother's breast inoculated (? from suckling the child). Pock ran a normal course. Mother had not been re-vaccinated.

Seventh week (20th April, 1907).—Child completely recovered.

Longet is careful to distinguish between spontaneous vaccinal eruptions (vaccinal eruptive fever) and multiplication of pocks by auto-inoculation. But, since the latter form of generalised eruption can occur without any pre-existing lesion of the skin (Acland), it must be a matter of considerable difficulty to differentiate between them clinically, and to eliminate, with any approach to certainty, the possibility of accidental inoculation. Apart from the fact that the first pock appeared on the heel, that the vaccinated arm was kept covered by a dressing, and great care taken to prevent contamination, the above case seems to have every claim to the title of vaccinal eruptive fever, for it agrees in many of its details with the salient points of that disease as outlined by Dauchez. Beginning on the ninth day after vaccination the eruption continued to appear in successive crops from the ninth to the fifteenth day, thus corresponding closely in point of time to a case reported by Fox. But there is a striking difference to be noted. In generalised vaccinia, following the rule of the exanthemata, to which it becomes comparable, there is pyrexia, varying in severity according to the extent and nature of the rash, the amount of local reaction, the presence or absence of ulceration, or other unessential complications. Besnier, however, holds that without some complication, such as glandular enlargement, pyrexia is absent. But it will be seen that all these predisponents are amply fulfilled in the

above summary, so that the absence of pyrexia already alluded to makes the case remarkable, and it becomes the more so when this association of apyrexia and excessive local reaction in the child is compared with the acute pain and marked constitutional disturbance aroused by the single aberrant, but otherwise normal pock, in the mother. The difference in constitutional derangement can hardly be accounted for by the fact that the child was vaccinated with calf lymph, and the mother with humanised lymph, because Acland's investigations have led him to the belief that vaccination with calf lymph tends to produce more severe inflammatory reaction than the same operation performed with humanised lymph. On the other hand, the age factor probably entered into the question, for "it is pretty well established that the constitutional disturbance (of normal vaccination) is much less in infancy than in later childhood, and less in very young infants (under one month) than in those of five or six months."

In seeking for a cause of generalised vaccinal eruptions we may attribute them to (1) the character of the virus employed ; (2) the character of the soil in which it is implanted ; (3) external accidents (including auto-inoculation). Given a healthy child, in good and wholesome surroundings, a lymph carefully selected and used, and full attention paid during and after the operation to aseptic requirements, the last-mentioned factor may not unreasonably be excluded. Our knowledge of the influence underlying the second factor is as yet purely conjectural. The personal equation shows too variable and unexpected a range to allow us to deduce direct pathological consequences from it. So that the character of the virus alone remains to be considered, and the matter resolves itself into an inquiry into the real nature of vaccinia, and the origin of these rare exacerbations in its virulence.

Although opinion has swung somewhat from agreement with Jenner's assertion as to the absolute identity of cow-pox and small-pox to the belief that they are closely allied diseases springing from a common ancestor, yet, until lately, no definite proof of their true relationship has been brought

forward. Not but that a vast amount of experimental research has been undertaken in an endeavour to solve the problem. The line first adopted was to introduce small-pox matter by some means or other into the system of the cow, with the view of thereby eliciting an attack of cow-pox, and so establishing the identity of the two maladies. A great number of the earlier efforts undertaken in this direction proved abortive, and, even when positive results were obtained, they were too anomalous, and too exceptional, to serve any useful purpose. More recently, however, with greater regard to cleanliness, attention to details, and the employment of calves in lieu of heifers and milch-cows, it has been possible to show that vaccinia is a final and invariable result of variolation of the calf, although the necessary number of removes from calf to calf may vary considerably in different series. In an endeavour to support this conclusion attention was next directed to the bacteriological side of the question, and various observers claimed to have isolated the specific organism. Pfeiffer was the first to throw doubt on the results of these investigations, and later Copeman was able to show that these micro-organisms belonged to one or other variety of staphylococcus, and their presence could in no sense be looked on as specific, or even essential. Copeman and Klein, in 1892, separately demonstrated the presence in vaccine and variolous lymph, as well as in sections of skin passing through a vaccine vesicle, of a small bacillus which was regarded as the active contagium of the diseases in question. But Wassermann proved by cultural methods that pustules may be free from bacteria; Perkins found no bacteria in a case of purpura variolosa, and Councilman has produced variola with material demonstrated to be free from bacteria by the most careful cultural tests. At the same time the last-named observer admits that bacterial infection plays a prominent part in the pathology of the disease, and believes it to be the chief agent in bringing about a fatal termination. In the same year (1892) Guarnieri described certain "vaccine bodies" which he found present in the epithelial cells of an inoculated area; he considered them to be protozoan organisms, and gave them the specific

name of *Cytoryctes variolæ*. However, his deductions did not meet with very general acceptance, it being held that these bodies were degenerate structures or by-products of the infected cell. But von Wasielewski in 1901 adduced further evidence in support of the protozoan nature of these cell-inclusions, and since then the work has been taken up by many American writers, notably Councilman, Magrath, and Calkins, who have elaborated the life-cycle of these organisms, and ably met all objections brought forward on the ground of the appearances being the result of accidental products. As a result of their careful experiments and logical deductions there now seems to be no reasonable doubt left as to the responsibility of these protozoan bodies in the production of both variola and vaccinia. At the present day, therefore, we are forced to agree with Jenner's first contention that cow-pox and small-pox are to all intents and purposes one and the same disease.

Like all sporozoa these vaccine bodies undergo definite reproductive phases, and both vaccinia and variola possess a common asexual life-cycle, carried on in the body of the epidermic cell. But in variola the process goes further, in that a second and more important life-cycle takes place within the nucleus of the cell, whereby the parasite is able to reproduce itself sexually, with the ultimate germination of spores. This sexual cycle is extremely difficult to follow, and various phases of it are more or less conjectural and analogical; but the vaccine cycle has been observed under the microscope from its initial to its final stage, and may be briefly delineated as follows :—

1. The organism is first seen in the cytoplasm of the epithelial cell as a minute, spherical, homogeneous body which is to be interpreted as a gemmule (*v. infra.*) derived by a previous reproductive process from the primary organisms. (Fig. II., 1.)

2. It enlarges (measuring about $3\ \mu$.), vacuoles appear in its centre, and, occasionally, a minute central dot, which stains deeply with methylene blue, but which cannot be regarded as a nucleus. (Fig. II., 2, 3.)

3. The organism continues to enlarge, and now a number of minute unstained spots appear in its periphery; these become larger, and take on a green stain with Borrel's reagent,^a whereas the rest of the periphery stains red. This red-staining material is the germ-forming material (protogonoplasm), which later gives rise to the reproductive bodies known as gemmules. (Fig. II., 4.)

In all three stages the organism (which always lies in a vacuole in the host cell) may be seen in various shapes, showing amoeboid movements, and protruding pseudopodia.

4. On attaining its full growth the adult amoeboid organism

FIG. II.

A schematic representation of the various stages of the vaccine cycle modified from Calkins.

has a diameter of 10–14 μ ., and consists of a finely granular protoplasm, with no nucleus, no vacuoles, and no inclusions except the red-staining protogonoplasm, which is usually in some stage of gemmule formation. (Fig. II., 5, 6.)

5. The protogonoplasm is originally in the form of granules, diffused through the body of the organism, and the gemmules are formed by the accumulation of these granules, and are liberated by the disintegration of the framework of the mother organism. (Fig. II., 7.) This disintegrated body remains as a residual structure (the cytoplasmic residuum) in the host cell of the skin, and persists there for some time after the gemmules (the reproductive bodies) are distributed. These

^a Borrel's stain is a combination of picric acid and indigo-carmin used after a preliminary staining with a saturated watery solution of magenta.

gemmules may then develop into new cytoplasmic organisms by infecting an adjacent cell-body (Fig. II., 8), or (in small-pox) they may penetrate the nucleus of the cell, and ultimately become germ-cells within the nucleus (intranuclear cycle).

“The evidence of every stage in this cycle indicates that in vaccinia and variola we have to do with the same organism, which, in vaccinia, has undergone some modification by means of which the nuclear phase is inhibited.” The intranuclear phase is found only in variola, where it follows the cytoplasmic cycle. It is much more complicated than the latter, and leads to an infinitely more active multiplication of the organism. Moreover, the spores, which are the products of the intranuclear cycle, are capable of being air-borne, whereas the gemmules, the products of the cytoplasmic cycle, are not air-borne, and can produce infection only through intermediate agents. Herein lies the explanation of the widespread infection which characterises variola, an infection which can be explained only by the assumption of rapid and varied modes of increase of the parasite.

As has been said, in vaccinia only the cytoplasmic forms of the parasite have been met with, and these show in their manner of multiplication an exact correspondence with the cytoplasmic forms of the variola parasite. As regards size and structure there are slight variations to be noted, but these “are not greater than will be shown by the same flowers in different gardens.” The inhibition of the nuclear phase marks a clinical difference that is obvious enough, but its causal significance remains unexplained. Certain it is that from the contents of a small-pox vesicle three forms of the same disease—variola vera, variola inoculata, and vaccinia—can be produced, any one of which confers immunity against all other forms. The difference in the course followed by the disease depends on the nature of the host (rabbit, calf, monkey, or man), the method of its introduction (inoculation, or air-borne infection), and, possibly, upon the stage of the lesion from which the virus is taken. And vaccinia is to be regarded as a true variety of the disease, although that variety may not be established at once. Tyzzer, indeed, produced inocu-

lated small-pox in a monkey with lymph which had passed through no less than five generations in rabbits, the virus being originally obtained from a case of inoculated small-pox in a monkey. The process of "removes" appears to result in some modification whereby the organism is prevented from entering on its intranuclear phase, and is forced to repeat itself within the boundaries of the cytoplasmic cycle. Are, then, these occasional outbreaks of generalised vaccinal eruptions to be looked upon as an effort on the part of the organism to throw off this unknown restraining factor, and revert once more to its compound sexual cycle? Apart from the well-ascertained fact that vaccinia rarely exhibits a tendency in this direction, it seems most unlikely, from a theoretical standpoint, that an under-vitalised form (provided that form has been properly established by a sufficient number of removes) should be able to display suddenly an exalted virulence in a single individual, without having first undergone a gradual process of recovery to its original life-cycle.

The explanation would really seem to be found in the amount of resistance offered by the host cells to the organism at the site of inoculation. *Cytorytes variolæ* is an obligatory parasite—*i.e.*, it develops within the living cells of a tissue, and is found only in connection with these. It is constantly found in developing lesions, it increases rapidly *pari passu* with the development of the lesions, which themselves increase in extent by continual infection of adjoining epithelial cells; but, after the lesions have reached maturity and the cells no longer offer a suitable nidus, the organism is no longer found. So that the more rapidly cell-necrosis is procured the more confined will be the limitations of the developmental area. On the other hand, when the necrotic process is retarded, the organism increases in the favourable soil, until ultimately a local lesion is produced, which extends deep enough to allow the organisms to gain an entrance into the blood, and this infection of the general circulation is notified by a general eruption, the organisms being carried as emboli to various situations of the body. In support of this contention it may be noted—(1) that revaccination in individuals in whom

immunity has been partially established runs through a hurried evolution (Cory), the accelerated development of the pocks preventing the completion of the life-cycle of the parasite; (2) that retardation of the pocks is often the precursor of a general eruption; (3) that a general diffusion of vaccine pocks may be produced if the virus is administered not through the skin, but by the digestive, circulatory, or respiratory systems; and (4) that spontaneous generalised vaccinia (vaccinal eruptive fever) is almost invariably associated with a more than usually extensive local reaction. Longuet has reported some rare cases of "vaccinal eruption by migration"—*i.e.*, generalised vaccinia without any local manifestation at the point of inoculation; but the possibility in these cases of the virus having been introduced directly into the circulation by a too vigorous insertion cannot be altogether excluded.

How the mother became infected it is impossible to say. The position of the pock—*viz.*, above the nipple—lends some support to the suggestion that it was due to direct contact with the pock which appeared on the infant's nose. But this pock aborted before it became a vesicle, and, though the organisms are present even at this stage of evolution, they are situated in the deeper cells of the epidermis (Councilman); besides which we have as yet no direct evidence to show that they are communicable to another individual until vesiculation has occurred. It seems more probable that, in spite of all precautions, the contagium was carried by the nurse's or mother's fingers from the child's arm to the nipple, and it is not unlikely that other organisms were introduced at the same time, a fact which might account for the initial resemblance to mastitis.

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ART. II.—*Calmette's Ophthalmalmo-reaction to Tuberculin.*

By GEORGE B. M'HUTCHISON, B.A.

It is often by no means easy, with the ordinary methods of clinical examination at our disposal, to detect the presence of the early stage of many tuberculous lesions; and whilst their insidious onset, so frequently associated with symptoms at once vague, ill-defined, and inconstant, enhances the difficulties of diagnosis, it serves to emphasize the importance of prompt recognition if treatment is to be carried out with increased chances of success.

There can be no doubt that, in hospitals and similar institutions, the subcutaneous injection of tuberculin has proved of great service in rendering the existence of these obscure lesions more apparent. Its adoption, however, as a diagnostic agent in general practice is, for the most part, precluded by reason of the restrictions which surround its administration, such as confinement to bed, methodical recording of temperature, weight, &c., and by the fact, lately insisted on, that the opsonic index for tubercle, with all its attendant tedious processes, be estimated at stated intervals. Realising both its usefulness and its disadvantages, several workers in France and Germany have been striving by experimental means to discover a modification of the test whereby the technical objections hitherto associated with its use would be overcome. Such a modification would have the effect of bringing the test within the reach of the general practitioner, and would be a welcome addition to our clinical armamentarium. Before proceeding