CYST FORMATION, ACNEFORM LESIONS AND HAIR GROWTH FOLLOWING INTRADERMAL INJECTION OF STAPHYLOCOCCI IN SENSITIZED RABBITS*

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In 1946 J. Boe (1) described the cutaneous reactions of rabbits sensitized to Staphylococcus aureus. The phenomena were similar to those described by Zinsser and by Dochez for the streptococcus (2). Intradermal injections of 0.1 cc. of suspensions containing one billion cocci per cc. in normal rabbits produced no or only transitory reactions. When such injections were repeated at intervals of nine or ten days the reactions became more intense and prolonged and consisted of large inflammatory nodules which suppurated and discharged. The reactions reached a peak of severity after 5 to 7 weeks after which they decreased in size. Both sensitization and the subsequent reactions could be induced by formalin-killed as well as by living organisms. In repeating Boe's experiments, the morphology of the reactions seemed worth description.

METHODS

The Oxford strain of Staphylococcus aureus which has been maintained on artificial media for many years was used and also a strain (L) which had been recently isolated by blood culture from a fatal case of brain abscess and which was preserved during our early experiments in blood broth. For injection twenty-four hour cultures on nutrient agar for the Oxford strain or on sheep's blood agar for the L strain were suspended in saline. Cocci were killed by addition of 0.2 per cent formaldehyde. After twenty-four hours' exposure the suspensions were washed with saline. New preparations were standardized by comparing their opacity with a counted suspension of killed cocci. A row of 3–5 intradermal injections of 0.1 cc. of a suspension containing one billion per cc. was made at each test. Injections were repeated in most animals at intervals of 9–10 days. Some were inoculated three times a week in an effort to accelerate sensitization. There were marked differences in the reactions produced by the killed and the living suspensions.

REACTIONS TO KILLED COCCI OF OXFORD STRAIN (GROSS APPEARANCE)

The first injection of killed cocci in seventeen out of twenty-two rabbits produced only a small macule which disappeared within a week. Five animals developed small papular or pustular reactions which were somewhat more persistent. Two of these animals had severe infections of an eye or an ear respectively which may have reduced their resistance. The second injection produced a 5 mm. inflamed nodule in only one out of twelve. Of nine rabbits carried on killed cocci for two months or longer, four became distinctly sensitized by the time of the seventh or eighth injection. When sensitized they show in one or two

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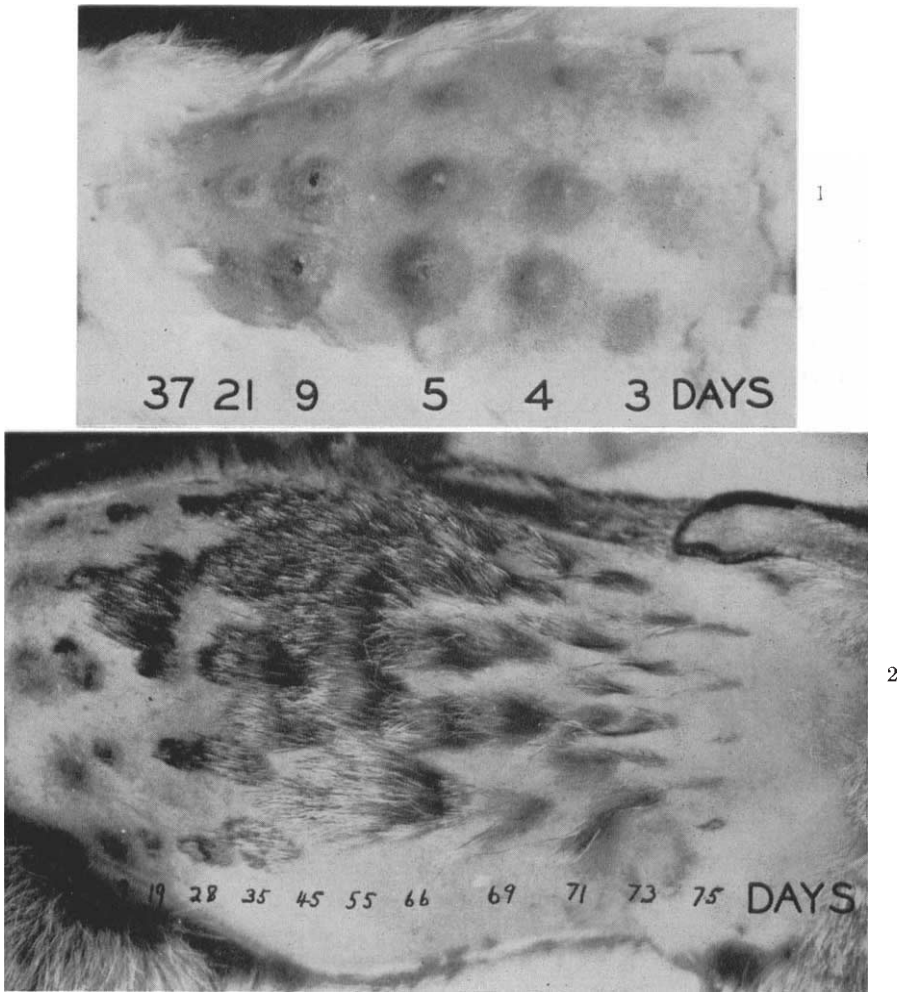

FIG. 1. Lesions from serial inoculations in sensitized rabbit. Horizontally: Top row Oxford strain killed; Middle row Oxford strain living; Bottom row L strain living. Vertically: Right hand row, three day old lesions and left of this, four and five day old lesions forming abscesses. Further left, nine day old lesions from live organisms have begun to discharge and twenty-one old lesions have completely discharged. Twenty-one day old lesion from killed cocci (top row) has formed cyst.

FIG. 2. Lesions from serial inoculations with live cocci of L strain 9 to 75 days previously. At left, nine and nineteen day lesions are becoming cystic. Twenty-eight day lesions show pigment ring and beginning hair tufts. Thirty-five day lesions have large hair tufts. Over forty-five and fifty-five day lesions these tufts have enlarged and fused. At extreme right seventy-nine day lesions from third injection in this rabbit, when it was only slightly sensitized, have produced only small wisps of hair.

days after injection hard red nodules 5 mm. or more in diameter (Fig. 1). The inflammatory reaction subsided in one or two weeks leaving a firm yellowish nodule 2–4 mm. in diameter in the center of which minute pores filled with

dry plugs could sometimes be seen. These nodules ruptured and discharged almost invariably within four weeks and sometimes before the cyst-like character was developed.

The reaction of hair growth was striking. Within two to three weeks a tuft of hair appeared in a ring around each point of inoculation. In gray rabbits their appearance was preceded by almost black rings in the skin caused by young, deeply pigmented hairs which had not yet emerged. These rings were often visible in ten days. The tufts usually enlarged peripherally until they merged into a solid island of hair covering the area of inoculations (Fig. 2). On shaving, however, one saw a bald spot at each point of inoculation which persisted for some weeks. These tufts rarely appeared after a first inoculation and their size increased with increase in sensitivity, i.e., with increase in the intensity of the reactive inflammation. When small they persisted for months as isolated groups of 15 or 20 long hairs.

REACTIONS TO LIVING STAPHYLOCOCCI

In our first experiments, live cultures of the L strain appeared to cause more severe reactions than did those of the Oxford strain, and it is probable that when first isolated this strain was the more virulent. Later on, no differences could be observed and the reactions to the two strains will be summarized together. As in the former series, in 17 of 22 rabbits the first injection caused transient macular reactions. Five developed nodules 1–2 cm. in diameter containing one or two pustules which underwent involution completely in about a week. Ten were reinoculated ten days later and of these, seven showed a marked inflammatory response with central suppuration or necrosis (Figs. 1 and 3). The remaining three showed larger papules than on first injection. Four of these animals which were injected thrice weekly showed some increase in reactivity two days after the first injection. In nine animals injections were continued for over two months, the lesions becoming more severe and more persistent. The peak of reactivity occurred in from two to eleven weeks after the first injection. The lesions in sensitized animals were large, edematous and often hemorrhagic. Their evolution was in general more rapid than was that of lesions produced by killed cocci.

CYST FORMATION (HISTOLOGICAL APPEARANCE)

The cyst-like character of the older lesions produced either by living or dead cocci in sensitized rabbits led us to study their development in histological sections. In a day, a large dense mass of leukocytes, often containing many eosinophiles, appeared deep in the corium well separated from the epidermis and resting hair follicles (Fig. 4). Usually this was solitary, but occasionally other smaller masses were seen at a short distance from the main lesion. (For brevity such masses will be called abscesses, although they lacked many characteristics of a true abscess.) Unless the injection was made in a region of active hair growth, in which case elongated follicles traversed it, the abscess contained no remains of collagen or of any cutaneous structure. Scattered leuocytes in varying number were seen outside the compact mass. Giant cells were never seen.

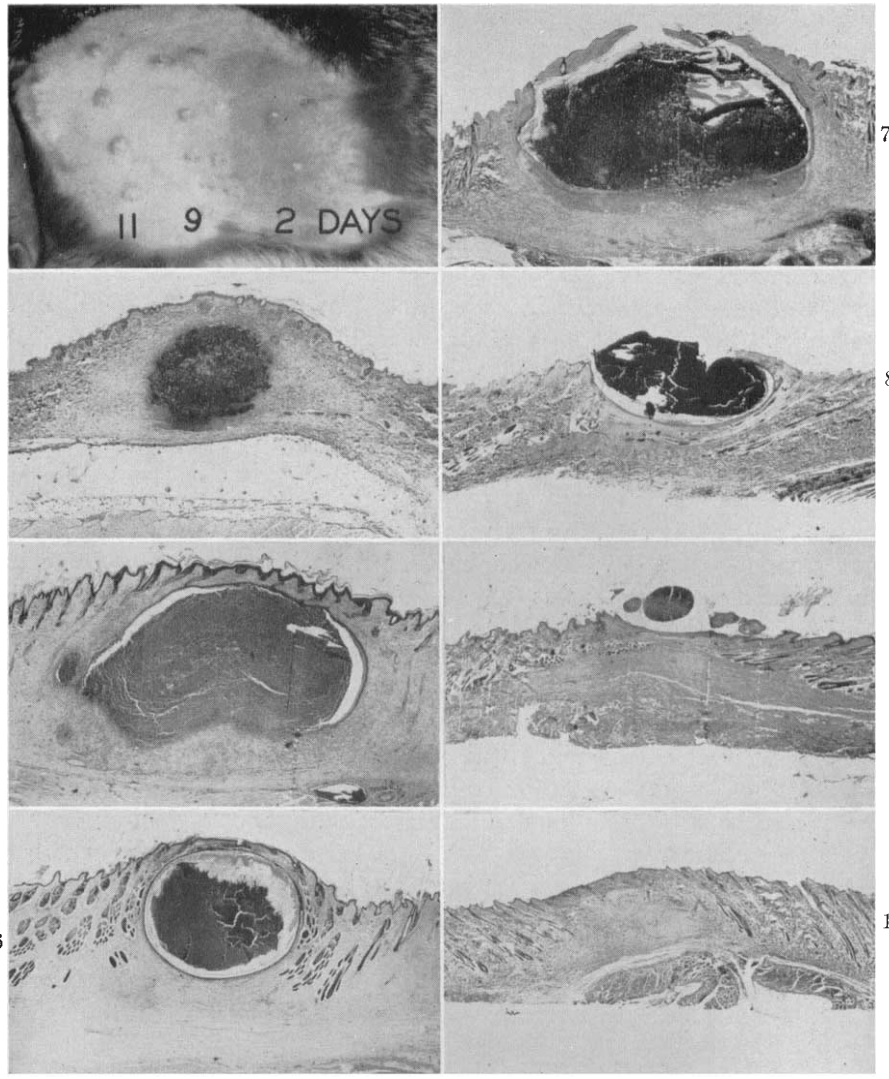

FIG. 3. Lesions from serial inoculations with live cocci of L strain in sensitized rabbit. Right hand row, two day old reactions, pustules with surrounding erythema. Middle row, nine day reactions, beginning cysts. Left hand row, eleven day reactions, well developed cysts.

FIGS. 4–10. Successive stages in evolution of cysts in sensitized rabbits. Speed of evolution varies in different animals and rupture of cyst was usually more rapid when live staphylococci were injected.

FIG. 4. Four day old lesion. Well developed abscess without epidermal wall, well separated from epidermis. Follicular dilatation and beginning down growth over abscess.

FIG. 5. Nine day old lesion (killed staphylococci). Epidermal wall around two thirds of abscess. Connection of cyst wall with follicle at center above. Increasing down growth of follicles at sides of abscess.

FIG. 6. Twenty-two day old lesion (killed staphylococci). Cyst completed. Hair follicles beside it have grown down below level of cyst.

FIG. 7. Eleven day old lesion (live staphylocci). Cyst wall not quite complete but ab-

Plasma cells appeared in increasing numbers toward the end of the first week. They accumulated about the abscess in streaks which appeared to follow the fibrous root sheaths. By the second week the abscess was usually surrounded by a thick wall of large round cells. These resembled histiocytes, but all gradations between such cells and typical fibroblasts were found.

The reaction of the epidermis was surprising. Injections were usually made in resting skin in which the hair follicles lay in clusters extending only about 0.1 to 0.3 mm. below the surface, their tips well above the leukocytic mass (Fig. 17). In one or two days those lying at the sides of the abscess elongated by an extension of the epithelial root sheath below the level of the hair (Figs. 18 and 19). The epidermal layer over the abscess became thicker in one or two days and it soon consisted of two or four layers of large cells, probably edematous, contrasting with one or two layers of cells with scanty protoplasm in the surrounding skin. This thickening of the surface epidermis increased gradually from the edges of the sections, becoming most marked over the abscess. By nine days there were marked acanthosis and hyperkeratosis of both surface and follicular epithelium. The follicular mouths were dilated and often plugged with keratin masses, the follicles greatly elongated and their cells large and hyperchromatic. As early as four days strands of epidermal cells were seen lying along the top of the pus. By the seventh to ninth day this epidermal wall often formed a roof over the abscess and extended part way down its sides (Fig. 5). In lesions two to three weeks old it completely surrounded the mass of disintegrating leukocytes (Fig. 6). This wall resembled the surface epidermis except that the cells contained more protoplasm. Basal, malphigian, granular and horny layers could usually be identified (Fig. 22). Numerous mitoses were seen near the tips of the down-growing strands.

The origin of this wall was apparently from one or more hair follicles. In serial sections from a twelve day lesion, an elongated and occluded follicle was seen spreading out over the top and side of an abscess (Figs. 11–16). Apparently it had ruptured so that the stratum corneum next to the abscess was continuous with the cells which lined the follicle (Fig. 14). Older cyst walls were often connected with several follicles, indicating that more than one took part in their formation.

In older sections where the epidermal wall had grown nearly or completely around the abscess, the leukocyte mass usually communicated with the surface through one or more small openings lined by epithelium and plugged by leukocytic debris (Fig. 7). In many lesions produced by living cocci the whole process was accelerated. A complete cyst was sometimes formed in 2 weeks but more

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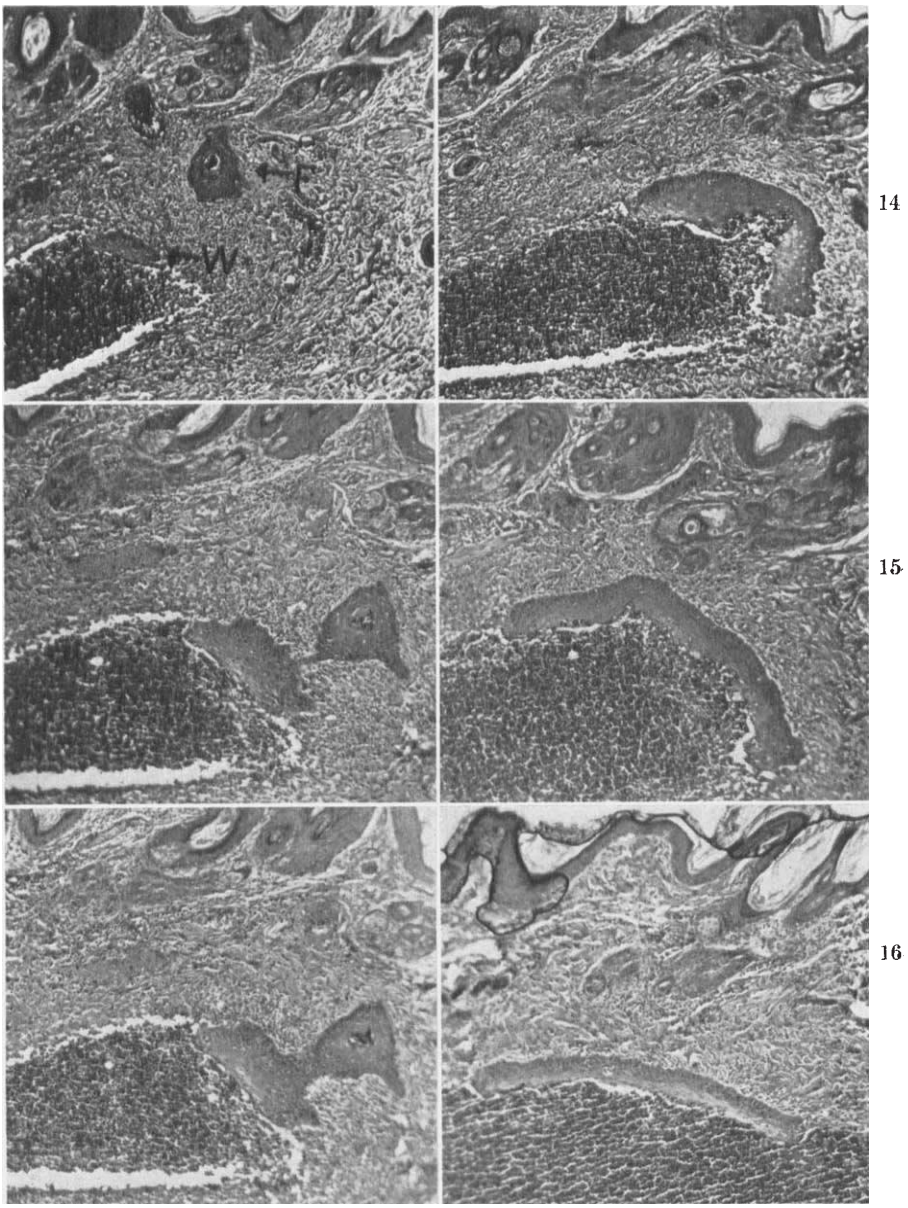
scess has already perforated the overlying epidermis in three places. A band of histiocytes lies under the floor of the cyst.

FIG. 8. Forty-four day old lesion (live staphylococci). Floor of cyst complete. Wide defect in cyst wall and epidermis above the leucocytic mass. New hair follicles at right have pushed under floor of cyst.

FIG. 9. Twenty-seven day old lesion (live staphylococci). Cyst almost completely evacuated. The floor has replaced the defect in the epidermis through which it discharged.

FIG. 10. Scar from inoculation 37 days before. Defect in epidermis replaced in center by hairless epithelium from floor of cyst. The scar is surrounded by a tuft of actively growing hair. Some horn cysts remain.



FIGS. 11-16. From serial sections of lesion from injection of killed cocci in a sensitized rabbit 12 days previously showing derivation of cyst wall from follicle.

FIG. 11. At F an occluded follicle. At W the tip of epidermal wall forming over roof of abscess.

FIGS. 12 AND 13. Follicle and cyst wall are connected

FIG. 14. Follicle has ruptured and inner wall is continuous with inner surface of cyst.

FIGS. 15 AND 16. Extension of epidermal wall over abscess

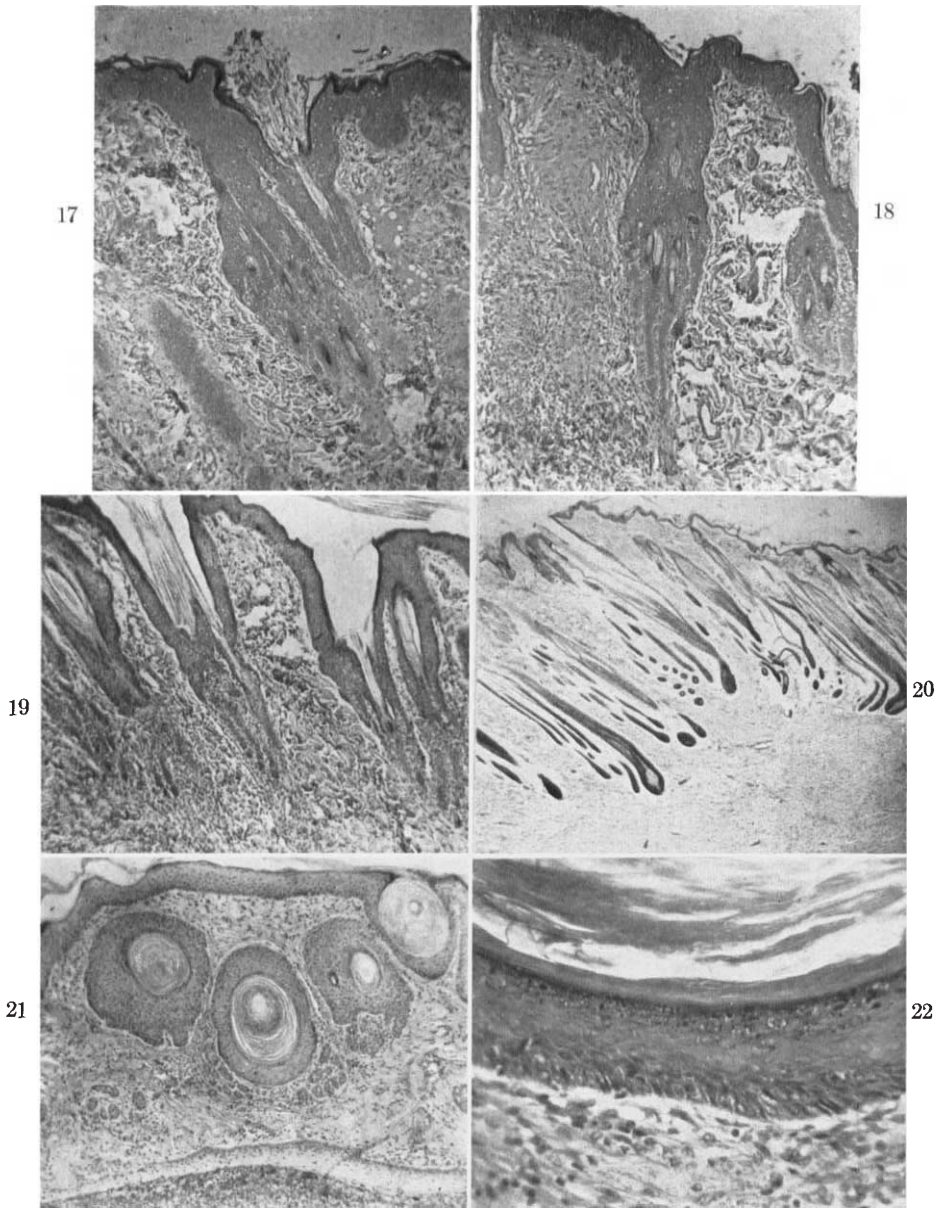


FIG. 17. Lesion from inoculation of live cocci 3 days previously. Resting follicle at distance from abscess shows hair bulbs anchored close to base of follicles. Contrast with Figs. 18 and 19.

FIG. 18. Same lesion slightly lower in magnification. Stimulated follicle near abscess shows root sheath epithelium streaming down from level of hair bulbs.

FIG. 19. Four day lesion showing down growth of root sheaths from follicles.

FIG. 20. Thirty-one day lesion. New hair has grown from elongated follicles forming tuft. Hair papillae visible just left of center and at extreme right.

FIG. 21. Nine day lesion from killed cocci. Horn cysts lying between surface epidermis and strand of epidermis which is growing over the roof of an abscess.

FIG. 22. Wall of cyst from seventeen day lesion showing differentiation into basal malphigian, granular and horny layers.

often the leukocytic mass was discharged through follicular openings before the cyst wall was completed. In others produced by living and in most of those pro-

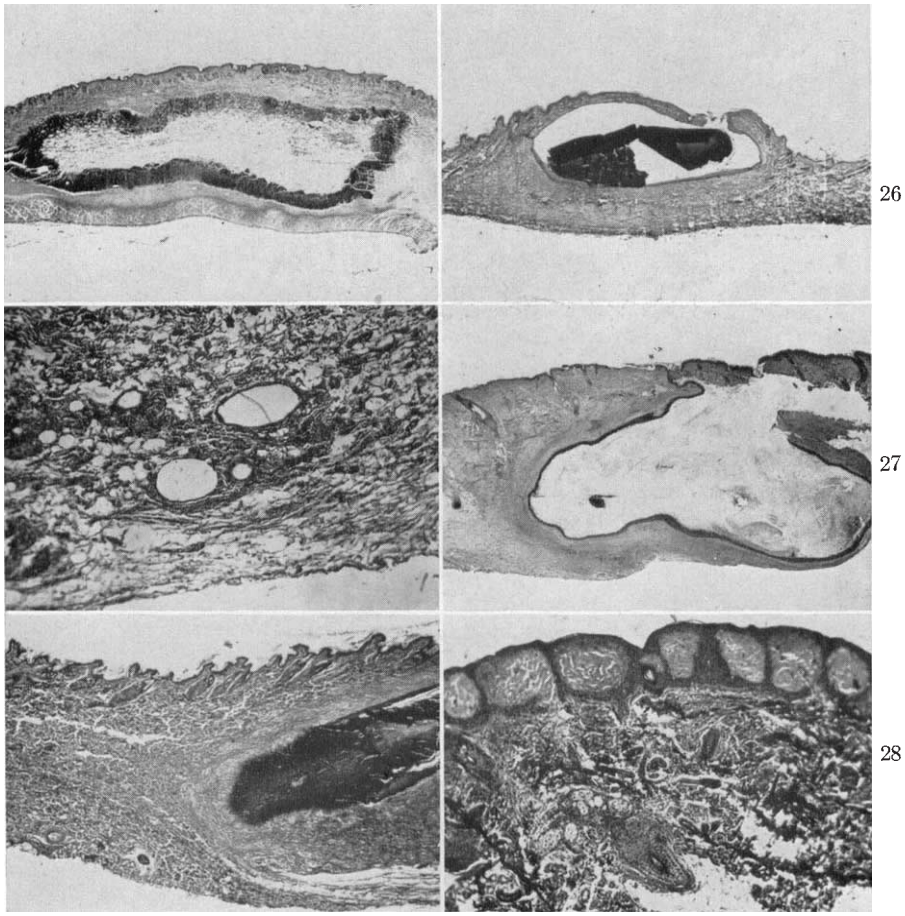


FIG. 23. Nine day lesion from turpentine injection. Huge abscess with no epidermal wall or evidence of epidermal stimulation.

FIG. 24. Thirty-eight day lesion from turpentine injection. Small cysts with endothelial (?) lining at base of corium.

FIG. 25. Twenty-eight day lesion from magnesium implant. Abscess with partial epidermal wall above and below at extreme right.

FIG. 26. Fourteen day lesion from inoculation with E. coli. Cyst with complete epidermal lining beginning to discharge.

FIG. 27. Cystic acne in human. Irregular cyst with epidermal lining, filled with desquamated epithelium, no pus.

FIG. 28. Colloid milium in human, showing sequestration of colloid masses by epidermis.

duced by dead cocci, discharge occurred after the wall was completed and the defect in the surface was filled in by the floor of the collapsed cyst (Figs. 8, 9, 10).

In a number of old nodules small abscesses were seen on which no hair follicle

impinged and which had no epidermal wall. None of these older naked abscesses were seen to penetrate to the surface and one was found intact deep in the corium 11 weeks after the causative inoculation.

Horn cysts lying immediately below the epidermis were also numerous in these sections (Fig. 21). They were most frequent above the abscesses where down-growth of the follicles was apparently obstructed. Their walls were thickened enormously and many were distended with rapidly formed horn cells. There were also numerous dilated and thickened follicles which remained open and were filled with horn plugs. These strikingly resembled comedones (Fig. 29).

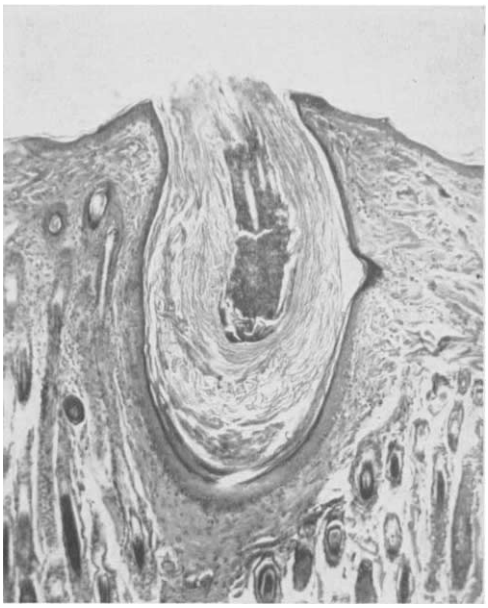


FIG. 29. Comedo-like plug in follicle near site of injection of killed staphylococci in sensitized rabbit 13 days previously.

Changes in the collagen varied. About some cysts the fibers appeared compressed in a concentric layer, but not increased in amount. About others there was a zone of delicate and apparently newly formed fibers. In some older lesions a small thick walled cyst with a tiny cavity filled with debris was found imbedded in a dense ring of scar tissue and some older abscesses which had escaped sequestration by the epidermis were surrounded by thick fibrous walls. A few large sinuses were seen between some cysts and the epidermis, but few new-formed capillaries were found. In general there was little evidence of the granulation tissue usually observed about abscesses.

HAIR GROWTH

Down-growth of solid strands of follicular epithelium was noted in one and two day lesions. In 2 to 3 weeks the growing follicles at each side of the developing cyst reached nearly to the bottom of the corium (Figs. 5 and 6). Those nearest

the anterior cyst wall curved around underneath it apparently following the course of the displaced fibrous root sheaths, though the latter could not be identified in section (Fig. 8). The follicle walls were thickened and their bulk distended the corium (Fig. 9). As early as 10 days well developed papillae and new hairs were visible. In grey rabbits the unprotruded hair was deeply pigmented, but no pigment could be seen in the root sheaths or epidermis.

CONTROL OBSERVATIONS

Staphylococcus Toxin: Unlike staphylococcus suspensions, the staphylococcus toxin described by one of us (3) produces large areas of necrosis when injected intradermally in normal rabbits. On repeated injection the animals become not sensitized, but immune, and their serums contain antitoxin which neutralized the toxin in vitro. Grossly there is nothing to suggest cyst formation after toxin injection in either normal or immune rabbits and one may conclude that the cysts here described were induced by the bacterial cells and not by the toxin.

Two rabbits were given a series of simultaneous injections of staphylococcus toxin and staphylococcus suspensions in different areas. Their resultant immunity to the toxin did not inhibit their allergic reactions to the bacterial cells, although such inhibition occurs in rabbits sensitized to streptococci (2).

Staphylococci in Normal Rabbits: The dose of staphylococci used in the previous experiments caused only slight reactions in normal rabbits and neither cyst formation nor hair growth ensued. By increasing the dose of live cocci (Strain L) ten times, large, suppurating and often hemorrhagic nodules were produced. These ruptured and discharged within two weeks and by three weeks only diffuse induration and scarring were visible at most injection sites. Tufts of hair appeared around these lesions as in the sensitized animals. Two rabbits which had each received one previous dose of staphylococci, but which could not have been highly sensitized, showed the typical beginning of an epithelial cyst at the site of one of these ten-fold injections. From this series fourteen lesions of from 3 to 44 days duration were sectioned and no other evidence of cyst formation was found.

Escherichia coli: Two rabbits were given three successive injections of formalized suspensions of E. coli of the same opacity as the staphylococcic preparations. The reactions were somewhat irregular but all ran a more rapid course than those to staphylococci. A few injections of live bacilli produced similar results. The first injection produced a pustule which discharged and healed in 1 to 2 weeks. Subsequent injections caused large dome-shaped swellings which discharged pus and healed usually in 2 to 3 weeks.

Ten lesions which most resembled cysts were sectioned. Some revealed naked abscesses but one showed a picture which resembled the staphylococcus cysts (Fig. 26). In another specimen it could be seen that an abscess had broken into a greatly hypertrophied follicle and dilated it so as to form what appeared like a cyst on cross section. In none of the colon lesions was there evidence of follicular epithelium growing down around an abscess as in the staphylococcic lesions. On the other hand one or two horn cysts and comedo-like plugs were seen and there was stimulation of the hair follicles and development of hair tufts.

The reactions to E. coli certainly showed similarities to those to staphylococci. Their evolution was so rapid that there was hardly time for all features of the staphylococcic lesions to develop and one could not be certain from these limited experiments that the two processes differed essentially.

Turpentine: One-tenth cc. of turpentine diluted from 1-5 to 1-10 in peanut oil in two rabbits produced in three days huge abscesses with no evidence of epithelial encystment or of stimulation of the root sheaths (Fig. 23). These underwent involution rapidly, but in one twenty-one day lesion hardly detectable to the naked eye innumerable minute spaces were found microscopically deep in the corium (Fig. 24). They were quite unlike the cysts seen in the staphylococcic lesions, but resembled those of a paraffinoma and may have

been reactions to the peanut oil. They were lined with one to four layers of cells which somewhat resembled compressed epithelium. As these were remote from any hair follicle it seemed more likely that they were endothelial. There was no thickening of the surface epidermis and the hair follicles showed little evidence of stimulation. Only one lesion produced by turpentine developed a tuft of hair.

Magnesium: Pels Leusden (4) produced epithelial cysts by imbedding fragments of magnesium in the ears of rabbits. We imbedded some 30 fragments of magnesium turnings of various size in the skin of one rabbit. Many were promptly extruded. Seven small nodules which had persisted 2 to 4 weeks were sectioned. Several showed abscesses without epidermal walls and one merely a cavity with a fibrous wall. One complete epidermal cyst filled with pus and one abscess with an epidermal wall partly surrounding it (Fig. 25) were found, but one could not tell whether the stimulus to the epidermis came from the magnesium or from the secondary infection. Most of the implants stimulated growth of hair tufts.

India Ink: A number of injections of India Ink 1-6 were made. Four nodules produced by such injections 5 to 21 days previously showed varying degrees of suppuration and fibrosis but no epidermal stimulation.

DISCUSSION

Two aspects of these findings seemed significant. First, the sequestration of an infected mass by follicular epidermis, its extrusion through a defect in the surface epidermis and the filling of this defect by the floor of the cyst appears to be a distinct type of defense mechanism which seems not previously recognized as such. Secondly, the similarity of these large cysts filled with pus, plasma cells and debris, the small horn cysts and the comedo-like plugs in dilated follicles to the lesions of acne in the human was so striking as to suggest that many lesions of acne and many follicular cysts, often loosely called sebaceous cysts, result from staphylococcic infection or sensitization. While our observations suggest this hypothesis they do not prove it.

Hair Stimulation: Evaluation of the hair tuft formation observed requires consideration of normal hair replacement in the rabbit as to which our information is fragmentary. In man this process is continuous with probable peaks of activity in spring and fall. Langer (5) observed that in the deer and chamois all the hairs in winter are Kolben or resting hairs. In spring the root sheaths elongate and become attached to papillae. New hairs grow up to the surface and the moult occurs. He stated that in domesticated animals the periodicity is irregular. In the mouse it is a short and fairly regular cycle—replacement occurring every six weeks. Königstein (6) stated that in the rabbit hair replacement is independent of the time of year.

In our own experience, when rabbits are shaved in winter occasional islands or long ribbons of thick skin with dilated follicles are seen. In white rabbits these islands appear as plateaus slightly raised above the surrounding thin skin. In grey rabbits they appear grey with an almost black border contrasting with the surrounding pale pink skin. The color, as Königstein noted and as our own sections show clearly, is due to pigment in sprouting hairs and not to pigment in the epidermis or root sheaths. Hair grows rapidly from these strips or islands of thick skin a few days after shaving, whereas the remainder of the shaved skin remains hairless for months. In spring we have found larger islands of thick skin which

spread until they covered most of the body, but we have no complete observations on the annual cycle.

Lutz (7) noted growth of hair tufts in rabbits after intense and sometimes destructive irradiation with ultraviolet light. Linser (8) and Linser and Kahler (9) described such tufts after application of tar, phenol, or chrysarobin, after curettement and after vigorous rubbing with plain vaseline. Flesch (10) has recently produced the dark spots which indicate incipient hair growth by rubbing with vaseline and lanolin. It is evident therefore that there is nothing specific about the effect of staphylococcic infection nor of staphylococcic allergy in the production of these tufts. Absence of such effect after most of the turpentine injections may mean only that the stimulus was too destructive or too transient.

The Cysts: We have found only two reports of the experimental production of epidermal cysts—one just mentioned by Pels Leusden (4) who used magnesium and one by Fischer (11) who used scarlet-red in oil. The former report was not illustrated and it is uncertain how closely the cysts resembled those produced by staphylococci. The latter pictured tumor-like downgrowth of solid masses of epidermal cells in irregular projections. Some small and some large irregular deposits of oil were surrounded by thin epidermal walls. His pictures also show general acanthosis, hyperkeratosis and hypertrophied follicles distended with masses of horn cells. Fischer thought his lesions due to a stimulus causing neoplastic change in the epidermis. Pels Leusden believed that epidermis tended to line any contiguous cavity such as a sinus and that his cysts were an expression of this tendency.

In these staphylococcic lesions, the acanthosis and hyperkeratosis of the epidermis, the downgrowth of the hair follicles, the encystment of the abscesses and the formation of follicular plugs and horn cysts all indicated the influence of some unidentified stimulant to epidermal growth. The proliferating epithelium might have been attracted to the abscesses or might have followed their periphery because growth there was unobstructed. The regularity with which epithelium lined the staphylococcic lesions in sensitized rabbits and its failure to do so in most of the defects produced by E. coli, magnesium or turpentine is evidence that the existence of a contiguous open space in itself is not, as Pels Leusden suggested, an adequate stimulus for epithelial growth of this type.

It has often been assumed that the so-called implantation cysts occasionally found in the palm after injury are produced from fragments of epidermis which have been buried in the cutis by puncture with some sharp object. Pels Leusden believed his experiments disproved this hypothesis. Certainly in our sections it seems evident that the cysts developed from down-growing follicles. Moreover, had they been formed by fragments of epidermis carried in by our needles some should have developed after inoculation with sub-effective doses of staphylococci. This was not the case.

Was the cyst formation a specific effect of the staphylococcus or of allergy? Staphylococci in sensitized skin produced at least partial cysts in most of the lesions examined and if killed staphylococci had been used and the lesion was over three weeks old the encystment was usually complete. In our control experi-

ments the small deep cysts produced by turpentine in oil seemed of quite different character.

On the other hand, one cyst produced by injection of E. coli in a sensitized rabbit closely resembled those produced by the staphylococcus, although there was evidence that it was produced by a somewhat different mechanism. A few lesions produced by large doses of staphylococci in rabbits only slightly sensitized or implantation of magnesium fragments accompanied by infection showed a picture indistinguishable from the early stage of the staphylococcic lesions. Consequently one cannot conclude that these cysts are specific effects of infection by staphylococci or that an allergic reaction is essential to their production. It seems more probable that staphylococci produce in sensitized rabbits a stimulus of the right intensity and duration to favor the complete evolution of this process.

The effect of this epidermal reaction seems clear. The sequestration of the leukocytic masses by follicular epithelium and their resultant extrusion from the skin surface seems a mechanism well adapted to eliminating this necrotic material from the skin. The long persistence of some masses of pus which escaped epidermal sequestration is further evidence of the utility of this process. Encapsulation of similar infected foci by new-formed connective tissue has been frequently described, but scant attention has been paid to the function of epithelium in this regard.

Is there an analogous process in human pathology? In colloid milium nodules of degenerated collagen in the papillary layer are frequently encircled by epidermal cells, but they are not extruded (Fig. 28).

In lichenoid amyloidosis also, deposits of amyloid in the upper cutis are frequently surrounded in a similar manner by epidermis.

The resemblance of these lesions to acne is far more striking. The follicular plugs are very like comedones and the horn cysts look quite like milia. If one allows for the difference in thickness of the epidermis and the entire skin in the rabbit these pus-filled cysts, frequently incomplete at the base and communicating with the surface through one or several follicular openings plugged with keratin, seem essentially identical in morphology with the lesions of cystic acne (Fig. 27). The accumulation of plasma cells is a minor point of similarity. On the other hand, follicular cysts of acne may contain only epithelial debris and no pus.

It is dangerous to attempt deductions as to etiology from morphological evidence. The role of hormones in the production of acne, while not completely analysed, is known to be basic in the etiology of this disease. We have no evidence as to whether hormones influence the production of these lesions in rabbits. There is, however, little doubt that the staphylococcus plays an essential role in producing the acne pustule and it has long been puzzling that large pus-filled cysts in acne are frequently sterile. An allergy to causative staphylococci might explain this. It may be significant that in the rabbit at least, allergic reaction to staphylococci is a potent and consistent stimulus to acneform changes even if similar changes can be produced less regularly by other means. It would seem that the possible role of staphylococcic allergy in acne needs further study and evaluation.

SUMMARY

1. Intradermal injection of staphylococci produced in sensitized rabbits thickening of the epidermis, down-growth of hair follicles, activation of hair growth and encystment of the leukocytic mass by epithelium derived from the hair follicles. In addition small horn cysts and follicular plugs resembling comedones frequently developed.

2. Similar down-growth of follicles and activation of hair growth was produced by various other stimuli, as has been noted by many previous investigators.

3. Similar though not identical lesions were produced in control experiments. It is improbable that staphylococcic allergy is the only mechanism that can induce such cysts, though it was certainly the most regularly effective of the stimuli which we employed.

4. The cyst formation appears to be a defensive mechanism. Its similarity to cyst formation in acne and to epidermal sequestration in colloid milium and lichenoid amyloidosis is discussed.

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DISCUSSION

Dr. Samuel M. Peck: During the war while I was on duty with the United States Public Health Service, we carried out extensive experimental, clinical as well as histologic studies of so-called occupational acne. Histologically, many

of our sections closely resembled the microscopic pictures which Dr. Hopkins has just showed us.

This was especially true of the tar acnes where we have quite a period of inflammation with pustular reactions but no evidence for the presence of pyogenic organisms could be demonstrated. I visualize the mechanism, therefore, as one in which we had a specific effect by the chemicals producing occupational acne, but not in the sense of a hypersensitivity. I went as far as to try to isolate a chemical substance from acne lesions and sebaceous material which might resemble petroleum hydrocarbons in its chemical structure to account for sterile acne lesions. The work which Dr. Hopkins has just presented throws an entirely new light on the possible mechanism of occupational acne.

In addition, the same sort of mechanism is responsible for these chronic recurrent cystlike lesions seen along the lower portions of the neck. They are actually reactions to an ingrown hair whose direction has been changed by previous infection. The question of sensitization playing a role also explains the good results which I have been having in certain types of acne from the use of gradually increasing doses of autovaccine.

DR. DONALD M. PILLSBURY: Some years ago, Kulchar, Sternberg and I worked with experimental rabbits and dogs and found a very marked relation between the age of the animal and the amount of infection produced after the injection of living staphylococci, which had been stepped up in virulence in the particular animal studied. We did not use any killed staphylococci, and I wonder if Dr. Hopkins found anything of the sort when he used living staphylococci in the younger animals? Is there a lesser tendency to cyst formation, because this was certainly true in the experiments we carried out?

DR. ALBERT M. KLIGMAN: Has desensitization been attempted in these animals? If it were possible to accomplish this, it would be exceedingly interesting to follow the course of events in desensitized animals who were reinoculated. One could thus establish perhaps the role that sensitivity plays in the causation of the cystic lesions.

DR. GEORGE C. ANDREWS: It is interesting that working in the same institution and being such close friends, I did not know that Dr. Hopkins was doing this work. My own paper fitted in well with this present paper, though it was more clinical than experimental. I would like to say that in the treatment of acne we have been using antibiotics. Many of the cases of acne proved to be pure staphylococcic infections, and the cystic, nodular and pustular cases responded to Terramycin and Aureomycin. Where all kinds of other remedies had proved a failure, the cases have responded to these antibiotics. One case of especial interest was that of a young boy of 15, who was listless, weak, running a WBC of 21,000, granular casts and albumin in the urine, with an evening temperature of 100–100.5, who had x-ray treatments and all sorts of other treatment with no results. I thought the white blood count was due to some other disease. The urologist and pediatrician could not explain this. He continued this way for about 3 months

when we started giving him sulfonamides in spite of the kidney and urine findings, without results. Finally we put him on Aureomycin and immediately he showed good results. He got entirely well after about 5 months on Aureomycin. Another similar case was a boy about 17, very much underweight because it was painful for him to eat; white blood count of 17,000, pus and albumin in his urine; and he cleared up completely on Aureomycin. These cases show that acne may sometimes be a purely staphylococcic infection in sensitized individuals.

DR. J. GARDNER HOPKINS (Closing Discussion): I was very much interested in Dr. Peck's statement. I have used staphylococcus vaccine in cystic acne for some years on account of one apparently brilliant result. I believe it does something, but the disease is so uncertain in its course that results are hard to evaluate.

Answering Dr. Pillsbury: Boe stated that after successive injections rabbits became increasingly sensitive to about the 12th or 17th week after which they became desensitized. We have not noted that. We have injected some animals for a year or for a year and a half and at the end of that time they were still pretty sensitive, although in some the intensity of the reaction fell off. This makes me very uncomfortable about the apparent therapeutic result. In the few intradermal tests by injection of vaccine in patients with cystic acne we have not found that they were sensitive and moreover, we have no good evidence that injections did desensitize them. However, clinically the vaccine seems to do something.