

General Character of Epidermal Papillomas Induced by Carcinogens on Mouse Skin as Disclosed by Transplantation. (25135)

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The epidermal papillomas arising on mouse skin exposed to tar or other chemical carcinogens are the most common of induced cutaneous growths, yet they have only of late been propagated(1). Those chosen for transplantation, as most likely to succeed, had persisted long after tarring; and they were transferred to deep sites in sucklings and weanlings. Six out of 8 of them grew progressively in both and were maintained in series. But the question arises whether they were representative of the generality of papillomas; for when situated on the skin these are protean in form, differ much in vigor, and nearly always disappear eventually unless stimulated by promoting agents. For these reasons it has seemed possible that they might be of several sorts. To learn whether this is the case many have now been transferred and studied.

Method. The tumors were induced in C strain mice, as previously, and with the same "Landsteiner tar,"—which greatly promotes the growth of papillomas. They were transplanted by trochar to subcutaneous situations in sucklings and weanlings, just as before. The tar was applied once a week to large areas on the back of numerous adult mice of both sexes until the first papilloma appeared, but only after longer intervals later, to lessen inflammation and bacterial infection; and the growths were transferred when large enough to provide tissue for several to many implantations. They then showed the usual diversity of form, some being broad-based or onion shaped or pedunculated, whereas others were as yet mere unerupted mounds that were papillomatous, as made plain by their palisade markings on vertical incision. The stained sections made of them, when enough tissue remained for this, validated their character.

Results. Most of the papillomas transferred were the first to have arisen as result of the tarrings and such growths are especially liable to undergo regression *in situ* if exposure to the carcinogen inducing them is discontinued soon

after they have appeared(2). Nevertheless they did as well in their new hosts as those that happened to be second to fifth in order of appearance on the tarred skin. Five out of the total 29 failed to yield growths on transfer, one of them because of purulent infection. Eight gave rise to carcinomas only, although when implanted they had looked in the gross like typical papillomas; but sections made later of 5 of them showed cancer to have been present as well. Three yielded growths of mingled character or gave rise to carcinomas in some animals and papillomas in others. Thirteen produced papillomas only (benign keratomas(1)). Cancers often derived from these after further transfer.

Every papilloma successfully transferred was passaged in order to learn more about it. Nearly all of the numerous growths thus obtained enlarged progressively and after a few months proved fatal, but very occasionally a small one stopped growing because it had keratinized completely. All of them proved to be of the same kind as the 6 originally propagated, and they manifested the same individual differences in capability. Eight out of 16 (counting the 3 in which a carcinomatous element was present) proved to be "able-bodied" papillomas (Type A(1)). They consisted of neoplastic cells which had retained the ability of normal epidermis to extend laterally on the bare wall of the graft pocket and to differentiate inwards, forming squamous, keratinized elements. These activities resulted in gradually enlarging cysts lined with a thin layer of papillomatous tissue and full of a dense mass of keratin. The other 8 papillomas were composed of cells that were crippled to a greater or less extent, both in ability to keratinize and to extend on the bare wall of the pocket in which they lay (Type C). These growths failed, more or less completely, to line the pocket, and they formed less keratin than the "A" growths. But the keratin acted as an irritant on the con-

nective tissue directly exposed to it, and the result was a cyst containing thin fluid with keratin suspended in it. The cyst had walls that were bare except for a papillomatous mound projecting into its interior, or a cauliflower, sometimes low and broad-based but often pedunculated and not infrequently almost entirely filling the cyst cavity. All gradations between A and C tumors occurred, and their cells did not differ significantly in aspect. Those of both growths underwent carcinomatous change about equally often. As a rule the A papillomas extended more rapidly on the walls of the enlarging cysts than did the cancers arising from them, and these latter could be left behind by a judicious selection of grafts at the next transfer. The C papillomas on the other hand failed to outstrip the cancers and hence were soon supplanted by them.

Dr. James S. Henderson of this laboratory has generously permitted a report here on the character of 12 epidermal papillomas he has recently propagated. Four were induced by tarring the backs of C mice and 8 by the repeated application of 20-methylcholanthrene in benzene or Crabtree's medium(3). All proved on transplantation to be of the kind just described and those of the A and C types were equally frequent.

Accident, infection of the grafts, or some host influence may have determined the failure of the papillomas that gave rise to no tumors after transfer. The many that succeeded have yielded growths that enlarged at much the same moderate pace,—a surprising fact in view of the activity that some papillomas manifest when situated on the skin and the indolence of others. Evidently local cutaneous conditions have much to do with this difference.

Conclusions. The transplantation of numerous epidermal papillomas induced by tar or 20-methylcholanthrene has shown them to be due to neoplastic changes of a single kind. Their wide diversity of form and behavior, when situated on the skin, seems referable in the main to differing capabilities of their cells. The great majority of them, indeed perhaps all, are transplantable in series, when favoring sites are provided them.

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 2. Mider, G. B., Morton, J. J., *Am. J. Path.*, 1939, v15, 299.
 3. Crabtree, H. G., *J. Path. and Bact.*, 1940, v51, 299.
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Experiments on Cholesterol Atherosclerosis in Rabbits.* (25136)

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Duff(1) suggested that atherosclerotic lesions may be due to impurities when rabbits are fed cholesterol over a long period. Recently Altschul showed that heated cholesterol (2) or dried and heated egg yolk(3) were more effective than cholesterol itself in obtaining atherosclerotic damage in rabbits, guinea pigs or hamsters, suggesting that com-

panions of cholesterol or products formed during heating were responsible. Nevertheless, most investigations on cholesterol atherosclerosis were made with commercially available, so-called pure cholesterol[†] which contained small amounts of impurities; (cf. 4). Experi-

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[†] Anitschkow and Chalutow(5) and Wacker and Hueck(6) reported feeding "pure" cholesterol ("reines Cholesterin") to rabbits. Study of original papers suggests that they really used commercial cholesterol. Their work, therefore, is not as conclusive as appears from Kritchevsky's book(7).