SUMMARY OF THE RESULTS OF EXPERIMENTS ON THE PATHOGENESIS OF EPITHELIAL GROWTHS

I. THE EXPERIMENTAL PRODUCTION OF MAMMARY CARCINOMA ON RABBITS

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In the course of the past five years in experiments on 188 animals, we have succeeded in producing twenty-three cases of cancroid and adeno-cancroid resembling that observed in man. These epitheliomata were produced by injection of liquid tar extract, pure tar, mixture of tar and lanolin, liquid paraffin containing tar, olive oil, or liquid paraffin, in the doses of from 0.3 to 0.5 cc., into the mammary glands; this injection was made once or twice a month. The animals which died after one or two injections are excluded. This development of epithelioma in 12.23 per cent of the animals injected might be considered a high average, especially when one recalls the fact that spontaneous mammary carcinoma seems to be very unusual.

TYPES OF MAMMARY CARCINOMA PRODUCED

We had expected a large, massive transplantable tumor in the mamma instead of a carcinomatous ulcer, such as is found on the ear in tar epithelioma. We found, however, that the secreting glandular epithelia do not respond to the irritation of the tar by proliferation, but soon perish. For this reason, we were unable to produce genuine glandular carcinoma.

Following injection of tar or tar-lanolin, the epithelium of the lactiferous duct and also that of the hair-follicles or surface epithelium reacted. Both of these have produced genuine cancroids. But the lactiferous-duct epithelia have also produced adeno-cancroids, whereby channels and cavities were formed.

1 Translated from the German by Dr. M. Ito.

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carrying linings of pavement epithelium and necrotic cells and
horny scales in the lumen. Sinuous or channel-like apophyses
lined with cubic cells may project from the wall.

HISTOGENESIS OF ARTIFICIALLY PRODUCED CANCROIDS AND
ADENO-CANCROIDS

Slye and Wells claim that spontaneous cancroids often appear
in the mamma of the mouse, which implies a metaplasia of the
lactiferous-duct epithelia into pavement epithelia. The site

of origin is either surface epithelium, follicle epithelium, or
lactiferous-duct epithelium, and the latter always undergoes a
metaplasia into pavement epithelium. It is difficult to demon-
strate whether these mammary cancroids originate in the sur-
face epithelium, follicle epithelium, or in the lactiferous-duct
epithelium, because they show no difference macroscopically or
histologically.
As a result of irritation, surface, follicle, or lactiferous-duct epithelia, first develop into horny cysts, or line horny cyst abscesses, or project as hill-like protuberances in the lumen of the lactiferous-duct, filling the latter with epithelial scales. From such epithelia an infiltrative growth in the surrounding loose tissue always arises, especially in the lanolin tissue, and finally an epithelioma results. The processes of the formation of adeno-cancroids are of greater interest. A certain kind of growth is often found which is very similar to the normal tissue, that is, short channels, which may be ramified, are formed near the alveola wall from the extended alveoli and tubules. The latter are filled with necrotic epithelium and leukocytes. Short plugs of pavement epithelium, or channels with cubical epithelium, may pass from the wall into the surroundings. Some-
times solid plugs consisting of metaplastic epithelium may be
tubulated by softening and liquefaction, so that passages lined
with layers of flattened epithelium are formed.

**HOW ARE MAMMARY TUMORS PRODUCED BY INJECTION OF**
**TAR, TAR-LANOLIN, AND OTHER AGENTS**

The spontaneous development of epithelial tumors was not
observed in the course of our work. This is shown from the
fact that the artificial tumors developed only at the site of injec-

![Image](image.png)

**Fig. 3.** Hill-like Hyperplasia of the Lining Epithelium in a Dilated lactiferous-duct in a Case of Adeno-cancroid.

tion, and that they did not result from a single injection, but
were caused by repeated injections. In other words, the longer
the period of experimentation, the more progressive were the
changes observed. It is probable, therefore, that the develop-
ment of these cancroids, like that of the tar cancroids of the ear,
is dependent upon the anaplasia which is brought about by
regeneration through the increasing hyperkeratosis. Other
factors inducing the development of adeno-cancroids are (1) the anaplasia of the lactiferous-duct epithelia, which are transformed into pavement epithelium and then proliferate, still preserving the passage-forming character; and (2) adenomatous hyperplasia due to regeneration of cells. We were unable to demonstrate a prosoplasia of the lactiferous-duct epithelium in adeno-cancroid from the mamma of the rabbit.

**SPONTANEOUS REGRESSION OF MAMMARY TUMORS**

Just as the epithelial tumors of the mamma of rabbits do not appear immediately after one injection, but develop gradually, they may also regress, thus differing from the mammary carcinomata of man.

We are able to report but one case of mammary carcinoma.

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**Fig. 4. Inguinal Lymph-node Metastasis in a Case of Adeno-cancroid of the Mamma.**

Nothing but alveoli with central softening are seen.
that existed in the animal over 1000 days; this animal died. We had another case, of shorter duration, in which there was a widely ulcerated surface, with a hardened border and a nodule, and metastasis to the inguinal lymphatic nodules, causing the animal to die of cachexia. In the remaining twenty-one cases, necropsy revealed newly developed carcinoma of relatively short duration, or residual cancer, or cancer which had been healed for some time. In the latter case, the healing of the cancer seems to have been expedited by repeated exploratory excisions, and the animals lived somewhat longer than those with newly developed or residual growths. Death was usually caused by marked emaciation or nephritis, or by other fatal complications. In our observations we have found that epithelial carcinoma pro-
duced artificially in an organ of a species not especially pre-
disposed to it, is more apt to regress than similar growths in man,
although once or twice the artificial growths showed structure
and biology characteristic of cancer.

RELATION BETWEEN GROWTH AND THE FREQUENCY
OF THE INJECTION

The number of injections required before cancer appeared
varied with the individual, so that an individual susceptibility
is an important factor.

We were unable to determine definitely the influence of age.
There is, however, a greater opportunity for the formation of a
tumor in animals which survive a longer period of treatment, as
was the case in experiments on tar cancroid on the ear of rabbits.
This indicates that the animals which are able to bear the tar irritation a greater length of time are more likely to develop cancer.

INFLUENCE OF PREGNANCY

It has long been known that the hormone of the ovaries has a great influence on the growth of the mammary gland; therefore it would seem probable that the growth of mammary carcinoma would be retarded to a certain extent by extirpating the ovaries (4, 5, 6). The stimulation of the ovarian function might therefore be assumed to excite mammary growth. In corroboration of this theory it was observed in our experiments that carcinoma was more often produced artificially in the animals which became pregnant during the treatment than in those which were not.
THE INFLUENCE OF LANOLIN-FEEDING ON THE DEVELOPMENT OF MAMMARY CARCINOMA

A lanolin-tar mixture when injected into the mamma is usually absorbed by endothelial cells, so that lanolin-cellular nodules or lanolin tissue develop. This condition is known as local lipoidosis. According to the histologic findings, the infiltrative growth of the atypical, hyperplastic, heteratopic, surface epithelium, follicular epithelium, or metaplastic lactiferous-duct epithelium, is apparently facilitated in the lanolin tissue. A remarkable feature in many cases was that, after the administration of lanolin had begun, the site of injection in the mamma soon showed a soft hill-like swelling. Sections from a similar portion of tissue revealed marked lipoidosis, whereby the atypical epithelial hyperplasia does not seem to be especially expedited. Here, however, one also observed that the infiltrative growth goes on more readily in the lipoidotic tissue, especially after the atypical hyperplastic process of the epithelium has already progressed to the infiltrative stage.

II. THE INFLUENCE OF LANOLIN-FEEDING ON THE FORMATION AND DEVELOPMENT OF TAR CANCROID ON THE EAR OF RABBITS

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By feeding lanolin in combination with the regular diet, okara (which is our usual food), before or during the application of tar, the folliculo-epithelioma often seems to be produced at an earlier stage than with control animals, but this is not always the case. One might maintain, from the result of the experiments, that it depends primarily on the individual susceptibility whether the folliculo-epithelioma develops at an earlier or later stage.

The growth of folliculo-epithelioma once produced, however, is accelerated by the lanolin-feeding, at least in combination with the application of tar on the ear of the rabbit. Local lipoidosis here also is more or less stronger than at the place where no applications of tar have been made. This apparently facilitates the
remote growth of the atypical hyperplastic epithelium, as evidenced by the histologic picture. One will also find that, under lanolin-feeding, developing folliculo-epithelioma more rapidly passes through the transitional stage to the pre-cancerous stage, and finally to definite cancer.

*Effect of lanolin-feeding on the nodules after the applications of tar have been discontinued.* The folliculo-epithelioma enlarged more rapidly with the beginning of after-feeding of lanolin, after the application of tar had been discontinued, than in the control cases in which the applications of tar had been made continuously, without feeding of lanolin. We have found that the folliculo-epithelioma is usually transformed into a cutaneous horn, that is, the more rapid development takes place in the

**Fig. 8. Another Region of the Case Shown in Figure 7.**
Short channels are seen leading from the wall of the epithelial cones.
form of a cutaneous horn, however not as a malignant transformation.

In accordance with the experience of Yamagiwa and Ichikawa, we observed that folliculo-epithelioma had a tendency to pro-

duce a cutaneous horny outgrowth, after the tar inunction had been discontinued. It seemed advisable, therefore, to make a comparison between the cases with lanolin-feeding and those in which the lanolin had been omitted after the tar inunction had been discontinued, and to use this as a control. The tar substance, which was applied once in both cases, must be cleaned thoroughly for this purpose. Our fourth experiment, which is still in progress, is of the above nature.

Result of the lanolin-feeding experiments with the painting of rabbits' ears with tar. Our experiments have shown that the
feeding of lanolin accelerates the development of the folliculoepitheliomas that have been caused by the application of tar. Consequently the change of character is also expedited. On the other hand, it must be remembered that the enlarging of

![Image](image_url)

Fig. 10. Another area from the specimen shown in Figure 9.
Note pearl formation, similar to glandular cancer.

the nodule is due more to the cutaneous horny formation than to the infiltrative remote growth. As Kon observed in his experiments on arteriosclerosis that general hyperkeratosis is produced in the animal by long-continued lanolin-feeding, so the local lipoidosis in our experiments seems to cooperate with the application of tar as a stimulant for hyperkeratosis. Hyperplasia of the follicle epithelia due to regeneration, and corresponding to the intensified keratosis, seems, on account of the local lipoidosis, to tend more readily toward deeper growth. We are unable to determine from our experiments just what is
the direct chemical influence of the constituents of tar and lanolin on the hyperplastic nature of the epithelial cells.

Fig. 11. Below, a Mamilla; above, Next to the Smaller Papilla, a Fistula.

The picture shows strong lipoidotic swelling around the place of injection resulting from lanolin-feeding.

III. THE RELATION BETWEEN LANOLIN-FEEDING AND THE FORMATION OF CANCROID BY PAINTING THE BACK OF A MOUSE WITH TAR

MASATOSHI KASHIWAGI, TAMOTSU FUKUDA AND JUNTARO OWAGA

Endurance of tar painting. Tsutsui had observed that the Japanese dancing mouse does not stand the application of tar as well as the English mouse, or the hybrid of the English and Japanese mice.

1 From the Pathological Institute at Tokyo.
The results of our experiments confirm this observation. Thirty-nine, or 83 per cent, of the forty-seven Japanese mice did not live longer than 100 days, while the remaining seven, or 15 per cent, lived over a period of 200 days after the first application of tar. The remaining animal lived 302 days. The English mice and hybrids (22 per cent of sixty-four animals) lived 250 days, 12 per cent as long as, or longer, than 300 days.

Relation between the endurance of the application of tar, and the frequency of occurrence of carcinoma. It is well known that, in man, age is a very large factor in the predisposition to cancer, and our experiments on the production of tar cancr oid show that this is also true in the mouse. Employing forty-seven Japanese mice, most of which quickly succumbed to painting with tar, we found that cancr oid was formed in but one, in which the animal fortunately lived 302 days. On the other hand, using
English mice and hybrids, which are able to withstand the tar painting better than the Japanese mice, twenty-seven cancroids were produced in experiments on sixty-four animals (42 per cent), and in a second series of experiments twenty cases of cancer were obtained from twenty-five animals (80 per cent).

*Incidence according to age.* The second experiment enabled us to ascertain the increased percentage of cases of carcinoma with the increase of the number of days the animals lived after the first application of tar. It, therefore, is possible to produce
cancroids in from 90 to 100 per cent without employing Bloch's special preparation of tar by merely using crude material, pro-
vided the animal is able to survive the treatment from 250 to 300 days.

*Influence of lanolin-feeding on the development of tar cancroïd in a mouse.* The feeding of lanolin in combination with tar painting was carried out in two series of the second experiment, and shortened the life of the small animals a great deal. With the usual diet a great number of animals (22 per cent) lived 250 days in spite of the tar painting; a few (12.5 per cent) lived 300 days. On the other hand, the animals that were fed with lanolin lived a much shorter life. From this alone it was evident
that the frequency of the formation of cancroid in mice, fed with lanolin, was considerably lower than in rabbits because of the early death of the mouse.

![Image of cancroid on the back of a mouse]

**Fig. 14. Tar Cancroid on the Back of a Mouse with Annular Infiltration on the Basis of the Flat-based, Conical, Horn-like Apophysis.**

*Forms of artificially produced cancroids.* The typical form of cancer in mice is a horn-like growth with a round base. It was usually evenly swollen and of a solid consistency, and had a

![Image of cross-section of cancroid]

**Fig. 15. Broad Basic Form of Tar Cancroid in a Mouse.**

*X* shows the border in comparison to the surroundings.
solid black horny mass in the center, which was somewhat pointed. The process began with marked hyperkeratosis and a downward infiltrating growth. In a few instances a form of cancroid with a wide base occurred, similar to tar cancroid on a rabbit’s ear, with an expansive, infiltrative growth in the skin, uniformly spreading in all directions. The horny mass over the cancroid tissue, or the upper part of the cancroid, is apt to necrose. Ulcer formation is also often observed.

REFERENCES


We wish to express our most sincere thanks to the Japanese Society for Cancer Research and the Imperial Academy of Sciences for their continued support in this work.