THE ENDOCRINE GLANDS IN EXPERIMENTAL CANCER
INDUCED BY BENZPYRENE

A STUDY OF THE RÔLE OF THE ENDOCRINE GLANDS IN THE PATHOGENESIS
OF TUMORS

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Certain pathologists (Fischer-Wasels and others) have advanced the theory that tumor formation is referable not to local tissue changes alone but to a general predisposition involving the organism as a whole. The exact nature of this predisposition has not been made clear. According to some investigators (Engel, Krasheninnikov, Elsner, Konsuloff, Brach, Kutcherenko, Fichera, and others) the endocrine glands play an important part in its production. This assumption, however, is based either on experiments with transplantable tumors or on the study of human pathological material, neither of which can be regarded as suitable for this purpose. In the transplantable neoplasm we have not an example of tumor origin from normal cells but merely of continuation of growth within a new organism. Human material, on the other hand, is usually derived from tumors in a fairly advanced stage and the picture may be complicated by secondary alterations in the glands due to destructive changes in the neoplasm, infection, general inanition, etc.

In order to elucidate the part played by the endocrine glands in the origin of cancer, it would seem appropriate to begin by observations while the disease is still in process of development. Should changes in these organs be demonstrable when cancer first appears, or even previous to this period, the question would then arise whether such changes are essential for the process of tumor formation in the body.

Beginning in 1929 we published a series of observations on the endocrine glands in the course of origin of tar cancer in mice. The results of these investigations may be briefly summarized.

In the precancerous period which follows immediately upon six months of tar painting, as manifested by the appearance of papillomata, morphological alterations are to be seen in the endocrine glands. In the thyroid the height of the follicular epithelium is reduced, indicating depression of function, as has been established, by physiological methods; on tadpoles occasionally nodal hyperplasia is observed. The thymus shows moderate atrophy of the parenchyma, especially in the cortex, while the parathyroids increase in volume with an alteration in the proportions of the different cell types, similar to that which is characteristic of older animals. In the suprarenals there is a decrease of lipoids in the cortex and an increase of lymphoid infiltration in the medullary substance; in some cases leukocytic infiltrations have been found in the cortex. In the ovary the production of graafian follicles is inhibited (Popova). In the intermediate lobe of the hypophysis, according to the investigations of Poly

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akov, cells with sharply pyknotic nuclei are present in increased numbers. No morphologic changes were observed in the testicles or in the islands of Langerhans in the pancreas.

Most of these alterations were found also in the early stages of tar cancer. In far advanced stages, with infection of the tumor and cachexia, the changes mentioned were intensified and several others were observed. There were a decided flattening of the epithelium and degenerative processes in the thyroid; complete atrophy of the thymus; the development, in part of the animals, of connective tissue in the parathyroids; a considerable decrease in the lipoid content of the suprarenal cortex; a distinct decrease in ripe follicles and an absence of corpora lutea in the ovaries; degenerative phenomena in the eosinophil cells and a slight increase in size of the chief cells in the anterior lobe of the hypophysis. Only in the testicles, the islands of Langerhans in the pancreas, and the cells of the suprarenal cortex could no manifest changes be observed.

Studies of the thyroid, parathyroid glands, and thymus in the advanced stages of transplantable adenocarcinoma and of spontaneous adenocarcinoma of the mammary gland in mice revealed changes similar to those described for tar cancer.

Nearly all of the changes observed in our mice as a result of tar painting were highly similar to those which appear in aging animals, leading to the impression that tar produces in mice a precocious "aging" of the endocrine glands.

For the elucidation of our main problem—the rôle of the endocrine glands in the pathogenesis of tumors—further researches were required. In particular it had to be determined whether the precancerous alterations and those observed in the initial period of tar cancer actually play a rôle in the production of experimental cancer of the skin.

One way of obtaining an answer to this question is by influencing the endocrine glands in various ways and making subsequent observations relative to the origin of cancer. The discovery of chemically pure carcinogenic compounds by Kennaway, Cook and their co-workers has made possible a more simple path of investigation. If in the course of producing cancer by application of pure carcinogenic compounds the same alterations should be observed as when tar is employed the probability of these being significant in the development of cancer would be highly increased. On the contrary, the absence of such changes would indicate that they represent merely a side effect of tar painting.

The present paper deals with the results obtained from investigations of the endocrine glands in mice subsequent to the application of 3:4-benzpyrene.

**Materials and Methods**

A single drop of a 0.5 per cent solution of benzpyrene was applied to the skin of mice in the interscapular region, once every three days over a period of three months. Towards the close of the third month papillomata had appeared at the site of painting in nearly all animals. The termination of the carcinogenic applications and the precancerous period thus coincided as to
time. As a rule, carcinomas were observed within two or three weeks after the appearance of the papillomata; rarely they appeared after a greater lapse of time, up to two months following the cessation of treatment. Morphologically the tumors were squamous-cell (mostly keratinized) carcinomas.

Three stages in the development of cancer were studied: (1) the precancerous period; (2) the period of early growth unaccompanied by distinct secondary phenomena; (3) the final period in the course of the disease which includes such secondary phenomena as dissolution of the tumor tissue, infection of the tumor, and general cachexia.

The benzpyrene applications were begun when the animals were three months old, so that the examinations were undertaken at from six to eight months of age. All mice belonged to the same strain, bred in the laboratory for a period of over ten years. The food consisted of milk and oats. For the study of the several glands from 20 to 37 animals were employed.

The controls consisted of endocrine glands obtained from a large number of normal animals used in our previous investigations, as well as the glands of 12 mice of the same age (six to eight months) subjected to the same conditions of existence as the experimental group.

**The Thyroid Gland**

The tissues were fixed with Zenker-formol solution and embedded in celluloidin; serial sections were stained with Heidenhain's hematoxylin or eosin-azur. The functional state of the gland was estimated for the most part by measuring the height of the follicular epithelium. For this purpose measurements were made, with an ocular micrometer, of 50 follicles of each gland and the mean value for the gland was computed. For further details see our earlier paper (1929); also Cramer (1928).

The data obtained are presented in Fig. 1. In 6 out of 9 mice in the precancerous period the average height of the follicular epithelium was within the
limits found in the controls, i.e. 8.5 to 10 μ; in only 3 mice was the figure lower than this. It is thus obvious that, though painting with a benzene solution of benzpyrene may produce a decrease in height in the epithelium of the thyroid gland, this change appears in part of the animals only, and even in these is slight. No significant morphological alterations were observed in histologic preparations of the thyroid. Nodal hyperplasia occurred in one case each in the experimental and the control series. In some glands, stained with Heidenhain's hematoxylin, the epithelium was found to contain an abundance of small granules of colloid matter. All this indicates that the function of the thyroid suffers no essential change from benzpyrene application, and that during the precancerous period the gland is in a more or less normal state.

In the presence of fully developed benzpyrene cancer (Fig. 1) the height of epithelial cells was found in most instances (12 out of 14) to correspond to the lowest limit of normal or to fall below this. Benzpyrene cancer thus seems to be responsible for a certain depression of the gland. This is more strikingly apparent with the appearance of secondary phenomena, when the height of the epithelium is less than 6 μ. In two cases of benzpyrene sarcoma, produced by introduction of benzpyrene in oil, examined in an advanced stage, the epithelium in the thyroid gland was found to be still lower. In such glands degenerative phenomena, as pyknosis of the nuclei, were likewise observed.

**The Thymus**

The thymus was fixed with formalin and weighed on torsion scales. Sections for microscopic study were stained with hematoxylin-eosin. As atrophy of the thymus occurs in mice without substitution by adipose tissue, it is possible to judge of the functional state of the gland by its weight. The data obtained by weighing are given in Fig. 2. As shown here, in 8 out of 10 animals
the weight of the thymus in the precancerous stage remained within the limits of individual fluctuations in normal mice six to eight months of age, that is from 10 to 27 mg. In 2 mice only was atrophy of the gland observed in the precancerous period. As was observed in a more numerous material, in connection with previous investigations, incidental involution of the thymus may occur also in control mice. Even admitting, however, that benzpyrene produces atrophy of the thymus in a small number of mice, the fact remains that in the great majority a normal thymus, so far as weight is concerned, is found in the precancerous stage.

The histologic picture of the thymus in the precancerous group, with the exception of the two cases mentioned above, was the same as in the controls. The thickness of the cortical layer was in accord with the age of the animal and the variations were such as are of common occurrence. The boundary between the cortex and the medullary substance in some mice of both the experimental and the control group was indistinct, and the medulla contained vast numbers of lymphocytes that had migrated from the cortex. The whole picture was that of normal involution in its initial and middle stages. In two of the benzpyrene mice the involution was more advanced.

In one third of the mice in which cancer was already established the weight of the thymus proved to be below normal; in another third it was on a par with the lower limits of the normal. In the remainder it was within normal limits. In the 6 mice in our series in which cancer had just arisen the thymus was found to have an average weight of 15.3 mg., i.e. only 3 mg. less than the mean weight of the controls, from which it may be concluded that experimental skin cancer does not produce rapid atrophy of the thymus. The process is gradual and is not simultaneous in all mice. On the other hand, it is equally clear that experimental skin cancer may not only be produced in mice with a well-developed thymus but may even grow intensively.

In cancer with secondary phenomena there was found, as might be expected, complete atrophy of the thymus. A similar observation was made on two mice with large benzpyrene sarcomas.

THE PARATHYROID GLANDS

As we had previously obtained evidence that tar painting produces an increase in size of the parathyroid glands and alters the proportions in which the chief cells are present in the gland, these points were made the subject of special study.

The dimensions of the glands were determined by measuring the surface of the largest section (that is, the mid-section). The outlines of the gland were reproduced on heavy paper by means of a camera lucida, and the portions of the paper bounded by the outline were cut out. The small pieces of paper thus obtained were weighed, and the relation between the weight of the pieces obtained from experimental and from control mice was taken as representing the relation between the surfaces of the mid-sections. The data obtained on males for the precancerous period and from controls are given in Table I.

As shown in the table, the range of variations and the average values obtained were similar for the two groups. Once this evidence was obtained, the
examination of subsequent stages—less interesting from the point of view of pathogenesis—could be omitted.

Evidence was obtained in our previous investigations that in the parathyroid glands of the mouse cells of two extreme types may be distinguished: type I, characterized by nuclei containing numerous chromatin granules; type II with a single large "complex nucleolus" consisting of a large body staining like chromatin, flanked by one or two small oxyphil bodies. The two types are linked by various transitional forms. In young mice the parathyroid is almost exclusively composed of cells of type I; in old mice cells of type II predominate, while mice of middle age occupy an intermediate position. We have elaborated an index expressing the proportions existing between the cells of type I and those of type II, based on counts made of all the cells occurring within one visual field at a magnification of 1000.

**Table I**: Relative Area of Mid-sections of the Parathyroids as Expressed in Weights of Pieces of Paper of Corresponding Size, in Milligrams

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The indices computed for mice (males) in the precancerous period were found to be as follows: 2.5; 1.0; 6.1; 6.4; 3.0; 3.8; 9.5; 2.3; 2.3; 2.6. The mean value (3.95) proved to be practically identical with the index previously obtained for normal males six months of age (3.8). The index shows considerable variation among individual glands both in normal and experimental animals.

From this evidence it appears that benzpyrene produces in the parathyroids no such changes as were observed following the application of tar. Since in mice painted with benzpyrene, cancer appears shortly after the appearance of precancerous phenomena, it can be asserted that experimental skin cancer may originate in mice possessing morphologically normal parathyroids.

No estimations were made of the size of the glands in mice in which cancer was already induced, nor were the indices computed. No significant histologic alterations could be observed in parathyroids in the presence of benzpyrene cancer.

**The Suprarenals**

The suprarenals were fixed and stained by appropriate methods for general examination (Zenker-formol; hematoxylin-eosin), determination of lipoids (formalin; Sudan III), and study of the chromaffine content (Wiesel's method with post chroming and Schmorl's method). Measurements of the cortical and medullary substance were made in the same manner as for the parathyroids.

The dimensions of the cortex as well as of the medulla were unchanged by benzpyrene application, even after the onset of cancer (Fig. 3). The area of the cortical substance in female mice was in most cases coincident with or even higher than the upper limit in males, confirming the observations of Masui, Tamura, Miller, Hett, and Deanesly that the suprarenals are larger
The lipoid content of the cortex in female mice remained unchanged both in the precancerous period and after the development of cancer, with no secondary phenomena in so far as it was possible to judge in histologic preparations. In males a slight decrease in lipoids could be observed in the zona glomerulosa and zona reticularis, in the precancerous period, though with the methods employed the significance of this was somewhat questionable. In the zona fasciculata the lipoid contents were always normal in males as well as in females. In the period of early cancer growth a diminution in the amount of lipoids was also observed in some of the male animals and in cancer accom-

panied by secondary phenomena this was sometimes striking in the zona glomerulosa and in the inner portion of the zona fasciculata.

The chromaffine substance in the cells of the medulla did not differ in the experimental animals from that in the controls. As in normal mice chromaffine cells made up a quarter to a third of the total number of cells of the medullary substance, being mostly arranged in groups on the periphery.

Thus, apart from the possible occurrence of a certain diminution of lipoid contents in the cortex in males, no morphological alterations were observed in the suprarenals in the precancerous period and in the presence of experimental cancer unaccompanied by secondary phenomena.

1 In the mouse it is the outer portion of the zona fasciculata that is richest in lipoids. In the cells of the zona glomerulosa in males about the same amount of lipoid is present, while in females the cells of the zona glomerulosa are poor in lipoids. The inner portion of the zona fasciculata contains less lipoid than the outer portion.

FIG. 3. SECTION AREAS OF THE CORTICAL AND MEDULLARY SUBSTANCES IN THE SUPRARENALS IN THE EVOLUTION OF BENZPYRENE CANCER, AS EXPRESSED BY THE WEIGHT OF PIECES OF PAPER OF CORRESPONDING SIZE

The black dots represent males; the circles females.
The functional state of the ovaries was determined by the number of large ripe follicles and corpora lutea present. The counts were made for the entire ovary, in continuous serial sections. As to the number of large follicles (Fig. 4) no essential changes occurred in the precancerous period or in benzpyrene cancer unaccompanied by secondary phenomena; in most of the animals the number of large follicles was within the limits of the control values. It must be noted, however, that the average number of large follicles in cancerous mice was smaller than in the controls (11 as compared to 18). In one mouse with cancer accompanied by secondary phenomena the ovary was found to contain no large follicles; in another they were present in small numbers and in a third the number was within the limits of the mean normal value. Thus, in advanced stages of cancer, a distinct inhibition in the function of the ovaries may sometimes be observed.

A somewhat similar picture is presented by the corpora lutea. The data obtained are given in Table II. In the precancerous period the number of corpora lutea approximates that in controls; after the appearance of cancer the ovaries were found in some, though not in all mice, to contain a reduced number of corpora lutea, and when secondary phenomena had developed corpora lutea were absent altogether.

Thus we find that in the ovary, as in other endocrine glands, the mere application of benzpyrene produces no phenomena comparable to those following the application of tar. On the other hand, the alterations in the ovary which appear as a result of a benzpyrene cancer are similar to those in tar cancer.

The Testicles

The testicles were fixed with formalin and frozen sections were stained with Sudan III and hematoxylin, or the material was embedded in celloidin-paraffin and stained with hematoxylin. No distinctly visible alterations were observed either in the precancerous period or when benzpyrene cancer had become apparent. In some mice with large cancerous tumors a certain diminution in the amount of lipoids in the interstitial cells was apparent, but as this evidence was obtained by evaluations made by sight it is scarcely possible to speak with complete certainty of its validity. In one case of cancer accompanied by secondary phenomena several tubules were found to contain degenerating epithelium; the spermatozoa in the tubules appeared to be diminished in numbers, but here also no striking alterations were observed.
In order to obtain the pituitary gland undamaged by contact with instru-
ments, the organ was fixed together with the base of the cranium and was ex-
cised from its bed only after treatment with absolute alcohol or celloidin and
oil. Fixation was with Zenker-formol, embedding in celloidin-paraffin. Com-
plete series of sections, of 4 μ thickness, were made and stained either with
Heidenhain’s hematoxylin or with azan.

A special cytologic study of the hypophysis of the mouse has recently been
made by Ourazov. Our observations in normal mice are in agreement on the
whole with the findings of that author. In the anterior lobe eosinophil cells
prevail, containing their secretion product in the form of granules. Much less
numerous are the basophil cells, which in mice contain no basophilic granules
but stain a diffuse light blue with azan. The third type of cell is the chief or
chromophobe cell.

The pars intermedia is composed in the main of uniform polygonal cells, in
the protoplasm of which fine orange granules are demonstrable with azan.
These appear to be identical with the elements described by Maurer and Lewis;
we consider them as chondriosomes. In young mice the nuclei of most cells in
the pars intermedia are poor in chromatin, which occurs dispersed in the form
of small granules. Together with these so-called "clear" cells, "dark" cells
have long been known to be present in the hypophyses of various animals
(Trautmann, Stendell, Benda, Bailey, and others). These cells are char-
acterized by a dark, pyknotic nucleus. According to Ourazov a connection
exists between the state of the cells of the pars intermedia which is accom-
panied by pyknosis of the nucleus and the secretory process, namely that
aspect of the process that is designated as holocrine secretion, and this point of
view we share.

As a result of a study of the hypophysis in mice, evidence has been obtained
that with age—from ten months onward—the cells with pyknotic nuclei grad-
ually increase in number, reaching a maximum at twenty-one to twenty-four
months of age, when they are arranged in large groups which sometimes oc-
cupy an entire visual field. As mentioned in the early part of this article, these cells were considerably increased in number in mice which had been subjected at a relatively early age (nine to ten months) to painting with tar (according to the investigations of our collaborator Polyakov). In tar cancer in a far advanced stage this phenomenon is still more marked.

Following application of benzyrene, on the contrary, there was no evidence of morphological alteration in any of the lobes of the hypophysis, either in the precancerous period or in the early malignant stage, either in females or in males. The several cell forms were present in the same relative proportions as in the controls and there was no indication either of an increase or a decrease in the secretory activity of the cells of the anterior lobe. No alterations in the pars intermedia or pars nervosa could be demonstrated by our methods.

In benzpyrene cancer accompanied by secondary phenomena, however, the pars intermedia was found to contain an increased number of cells possessing a highly pyknotic nucleus, i.e. cells in a state of holocrine secretion, while the anterior lobe showed alterations involving a small number of eosinophils, consisting in pyknosis of the nucleus and homogenization of the protoplasm, both presumably degenerative phenomena. In addition there was observed in far advanced cancer, both in females and males, a certain increase in numbers (hyperplasia?) of the chief cells, a phenomenon which was present in a less conspicuous form in tar cancer. Pictures of this sort appeared along the border of the gland where the anterior lobe merges into the pars intermedia.

Thus it may be concluded that in the hypophysis, as in the other glands, no alterations were produced by benzyrene application such as had been observed in tar experiments, though in far advanced stages of benzpyrene cancer analogous changes occurred.

The Pancreas

In all cases two portions of the pancreas, the head and the tail, were studied. Tissue fixed with Zenker-formol was embedded in celluloidin-paraffin and sections were stained with Heidenhain's hematoxylin and azan. Several pieces were fixed in Lane's solution and stained after the method of Bensley.

The main criterion employed for estimating the endocrine function of the pancreas was the diameter of the islets of Langerhans. The number of islets in a section in normal mice is so variable that it was considered of no interest to count these in the experimental animals.

The mean value of the diameter of the islets of Langerhans was computed from measurements made with an ocular micrometer at 150 magnification. If 25 islets could not be found within one section the measurements were continued in another section, skipping at least 10 sections. As the islets were sectioned in various planes, the figure obtained cannot be considered as the exact mean diameter. It is rather a conventional criterion, which with uniform application may be employed for making the necessary comparisons.

The data obtained for the mice examined and the mean values computed for groups of animals presented no essential differences from those of the controls. Nor was any difference observed between the sexes. Microscopic investigations presented no evidence of structural alteration of the cells.
Summary and Discussion

In the experiments recorded it has been shown that in mice painted with a pure carcinogenic compound, benzpyrene, which is presumably the main cancer-producing agent in tar, no morphological alterations of distinct and essential nature are apparent in the endocrine glands either in the precancerous period or in the presence of cancer in an early stage.

Secondary alterations in the endocrine glands which appear in advanced stages of benzpyrene cancer are identical with the changes that occur in tar cancer. Thus in benzpyrene cancer, as in tar cancer, there are flattening of the follicular epithelium in the thyroid, atrophy of the thymus, diminution of the lipoid content of the suprarenal cortex, a decrease of the number of large follicles and of the corpora lutea in the ovaries, increase in numbers of cells with pyknotic nuclei in the pars intermedia of the pituitary, and a somewhat larger number of the chief cells in the anterior pituitary lobe.

Our observations on the endocrine changes associated with experimental cancer are in general agreement with the findings of other authors (Babès, Twort, Lamma, Oike). At the same time they present certain differences, especially as compared with the work of Babès.

It must be stated that many of the secondary changes in the endocrine glands that have come to our observation have been described by various writers in malignant tumors in man, as for instance the atrophic changes in the thyroid, thymus, and ovaries, and the diminution of the lipoid content of the suprarenal cortex. The secondary alterations in the endocrine glands that occur in animals bearing various tumors are presumably similar in their character.

As mentioned at the beginning of this paper, many of the striking changes observed in advanced stages of experimental cancer were seen in a less accentuated form as a result merely of tar intoxication. In our experiments an
approximately similar picture was present in old normal mice. It is an interesting observation that those glands (medullary substance of the suprarenals, islets of Langerhans) in which no phenomena of "aging" appeared in the course of our investigations were equally unaffected by tar painting.

The fact that in tarred mice alterations in the endocrine glands appear even before cancer has become apparent, similar to those which develop physiologically with age, and the further fact that, as a rule, in mice resistant to the induction of tar cancer no alterations are found in the endocrine glands, induced us some years ago to suggest that the endocrine changes constitute one of the components of so-called general cancer predisposition and that the general predisposition produced (presumably) by tar is analogous with so-called "age predisposition."

On the basis of our experiments with a pure carcinogenic hydrocarbon, we are obliged to reject the above hypothesis, for it has been found that experimental skin cancer may originate not only in an organism possessing an endocrine system altered in a similar way as in senility (tar experiments) but that it may arise also in organisms in which the endocrine glands present no morphologically discernible changes (benzpyrene experiments). In our opinion absence of morphological changes indicates absence of essential functional alterations, but a study of the problem with physiological methods is most desirable.²

Since, then, experimental cancer of the skin develops both in the presence and in the absence of endocrine changes, it may be assumed that the state of the endocrine system plays no important part in the origin of this form of neoplastic growth. The alterations in the endocrine system are apparently not essential components of the "general cancerous predisposition," which, according to numerous authors, is an indispensable condition for the origin of malignant tumors and which may be produced, for instance, by tar.

The changes brought about in the endocrine glands by tar seem to be of no essential importance in the origin of tar cancer, but rather an additional effect of tar application, due to certain non-carcinogenic components of that complex substance.

It must be conceded, however, that while we may deny the necessity of preliminary changes in the endocrine glands in one form of cancer, such as the flat-celled experimental cancer of the skin and the corresponding professional skin cancers, this does not mean that the same is true of other types of tumor induced by other extrinsic chemical substances introduced into the body. Our data, however, render such a conclusion highly probable. As a matter of fact, by applying benzpyrene, sarcomas as well as carcinomas of the mammary glands, of the lungs, and of the kidney may be induced.

Our conclusions cannot, of course, be unreservedly transferred to the so-called spontaneous tumors. If the hypothesis, recently suggested, that "spontaneous" tumors arise as a result of the action of carcinogenic substances of endogenous origin proves to be true, then in the formation of such tumors

² We already have some such data at our disposal. Evidence has been obtained by our co-worker, M. Tchertkova, that oxidation processes in the body which, it is known, are dependent upon the function of the thyroid gland, remain unaltered in mice and rabbits painted with benzpyrene until the actual development of benzpyrene cancer.
three periods will have to be distinguished: (1) a period of formation of carci-
nogenic substances within the body; (2) a period in which these substances
produce their effect and tumors appear; (3) a period of tumor growth.

Experimental cancer induced by carcinogenic compounds embraces the
second and third periods only, since in this instance already formed cancero-
genic substances are introduced into the body. In transplantable tumors on
the other hand, only the third period is present—namely that of the growth of
tumor cells already present.

On the basis of our experiments we can only say that in the second period
of development of so-called spontaneous tumors in animals and man—i.e.,
when carcinogenic substances according to the present-day hypothesis are al-
ready formed—the endocrine glands apparently play no important part; at
least no preceding alterations in the glands are necessary. In other words, it
is not by way of the endocrine system that the action of carcinogenic com-
pounds is effected.

The rôle of the endocrine glands in the first period—that is in the process
of formation of carcinogenic substances—is quite another question, requiring
special study. Considering the suggestion (Kennaway, Cook) that such sub-
stances may be formed as a result of deranged metabolism (in respect of sterols
for instance), it may be assumed that the endocrine glands in their quality of
metabolism regulators are of no slight importance in this process.

Conclusions

1. In tarred mice various alterations take place in the endocrine glands,
similar to those which appear in old animals.

2. When, instead of tar, a chemically pure carcinogenic compound, benz-
pyrene, is applied, no such alterations are observed.

3. There is no reason to suppose that alterations in the endocrine system
are a necessary condition for the origin of tumors induced by chemical agents
introduced from without. The contrary is rather the case: in the pathogenesis
of such tumors the state of the endocrine glands is of no essential importance.
It is not by way of the endocrine system that the action of carcinogenic com-
pounds is effected. This statement does not, however, exclude the possibility
of a participation of endocrine glands in the process of the origin of spontane-
ous tumors, namely, in the hypothetical period of the formation of endogenous
carcinogenic substances.

4. In experimentally induced cancer of the skin, a series of secondary
changes due to the presence of the tumors occurs in the endocrine glands.
These changes are in many respects analogous to those which other authors
have observed in tumors in man.

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