Fluorescence Studies on Cancer*

I. Porphyrin Metabolism, Harderian Gland Fluorescence, and Susceptibility to Carcinogenic Agents

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It is well known that different species (8, 14, 35, 36, 44) and different organs and tissues (45) vary greatly in their susceptibility to carcinogenic agents. The only animals that have been extremely susceptible to the induction of tumors by means of physical and pure chemical agents are mice and rats. It has been found difficult and frequently impossible to produce tumors by the same methods even in other rodents (36). Shear (36) lists several investigators who found rabbits and guinea pigs refractory to the action of carcinogens that are potent in mice. By the administration of relatively tremendous quantities of methylcholanthrene, tumors have been induced in cottontail rabbits (39). Shimkin and Mider (37) induced tumors in a relatively high percentage of guinea pigs by subcutaneous injection of large doses of methylcholanthrene. From a tabulation of their own results and those of others (23, 33, 42) they state that, "... the relative carcinogenic potency of 20-methylcholanthrene, 3,4-benzpyrene, and 1,2,5,6-dibenzanthracene in guinea pigs is the same as in mice and rats (Fieser) but that guinea pigs are more resistant to the induction of subcutaneous neoplasms with these agents." Monkeys continue to resist the most drastic treatments with chemical carcinogens (1) and estrogenic compounds (1, 13); in the human subject, 3,4-benzpyrene has been used to treat 22 spontaneous neoplasms and 7 cures were described (2).

It has been postulated that certain unique features in the porphyrin metabolism of rats and mice are responsible for the extreme sensitivity of these animals to carcinogenic agents. The early observations (18) relating porphyrin metabolism and red fluorescence of the harderian gland to cancer susceptibility were limited to mice of inbred strains and of known susceptibility to spontaneous mammary carcinoma. There was some indication that the protoporphyrin 9 (type III) and coproporphyrin type I, which were responsible for the red fluorescence, were not formed in but merely excreted by the harderian gland (9, 21). The excess porphyrins excreted by the harderian glands were presumably produced in, or accumulated in, the mammary glands, lungs, skin, or subcutaneous tissues, which are most susceptible to spontaneous tumors.

The material included in the present report resulted from a study of the excretion of porphyrins by the harderian glands in other rodents and a number of other mammals. This investigation revealed that only the animals most susceptible to experimentally induced cancer (mice, rats, and hamsters) have red-fluorescent harderian glands that excrete porphyrins. The possibility that porphyrins of metabolic, parasitic, or chemotoxic origin are related to the high cancer incidence in certain organs and tissues in the human subject has also been examined. These studies have involved collaboration with clinical investigators and the results will be published in a series of reports. This first paper of the series will therefore include a comprehensive discussion of the hypothesis, a comparative study of harderian gland fluorescence and cancer susceptibility, and an outline of the general trend of the several investigations to be reported.

According to the hypothesis, cells and tissues subjected to abnormally high (optimum for sensitization) concentrations of certain porphyrins become hypersensitive to the action of normal as well as abnormal growth-stimulating factors or to relatively weak, natural, or artificial carcinogenic stimuli. The specific porphyrins that appear to have such a sensitizing

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action are protoporphyrin 9 (type III) and coproporphyrin type I, but perhaps other porphyrins or their pyrrol degradation products may have a similar influence. These substances may all be derived from abnormal decomposition of hemoglobin, catalase, cytochrome c, or other heme substances. An interference with the normal synthesis of these heme compounds would also result in an accumulation of excess porphyrins. For additional data on normal and abnormal origin and metabolism of porphyrins the reader is referred to reviews of this subject (7, 11, 21, 41, 43). These sensitizing pyrrol compounds may exert their influence either within the cells where they arise or on the cell surface of other cells after diffusion or transportation.

One line of investigation that has been followed in the studies to be reported has been directed toward a search for the presence of abnormally high concentrations of porphyrins in the organs, tissues, and species that exhibit a high cancer incidence. This line of investigation has disclosed some general relationships that have been summarized as follows:

1. Protoporphyrin 9 (type III) and coproporphyrin type I have been found in abundance in young or rapidly growing, but not in mature non-growing tissues. This evidence was derived from the literature on porphyrins.

2. The porphyrin metabolism, as indicated by the fluorescence of the harderian gland, varied greatly in rodents and other orders of mammals. There appeared to be a definite correlation between the excretion of excess protoporphyrin 9 and coproporphyrin I and the susceptibility to experimentally induced cancer. The areas where these excreted porphyrins accumulated in and on the skin of the animal (Plate I) coincided with the areas that, according to numerous investigators (3, 4, 26, 28), gave rise to tumors when the entire animal was irradiated with ultraviolet light.

3. In the human subject certain sebaceous glands excrete protoporphyrin 9 and coproporphyrin I, the same porphyrins as those excreted by the harderian glands of some rodents. The areas of the skin where the red-fluorescent sebaceous secretions are most commonly found correspond to the areas where the incidence of skin cancer is highest.

4. Red-fluorescent exudates were found to occur frequently and intermittently on the cervix of the uterus and other parts of the genitalia of women (29). It has been shown by extraction and analysis that the red fluorescence of these exudates was due to the presence of protoporphyrin 9, small amounts of coproporphyrin, and other porphyrins (19). Most of the evidence indicates that these porphyrins resulted from decomposition of blood.

5. Some of the pathogenic bacteria and numerous saprophytic bacteria and molds produce porphyrins that may be partly responsible for the high cancer incidence in the areas where these organisms exist over long periods of time.

There is no evidence to indicate that abnormally high concentrations of porphyrins have a carcinogenic action. The porphyrins appear to sensitize the cells to the action of carcinogenic or growth stimuli that would not induce atypical growth in the absence of porphyrin sensitization. As sensitizing agents to carcinogenic stimuli, it is not necessary for the excess porphyrins to persist after the malignant transformation has occurred. No systematic attempt has been made to demonstrate porphyrins in neoplastic tissues but fluorescence examinations have shown porphyrin to be present in some neoplasms (chloroma, necrotic centers of tumors, and on the surface of necrotic exudates of cervical carcinomas). Most of the malignant tumors that have been examined were not red-fluorescent and the porphyrin content was not determined.

METHODS AND MATERIALS

The observations on the harderian gland fluorescence have extended over a period of three years and were carried out on a very heterogeneous group of animals. These were usually discarded animals or animals killed at the termination of other experiments. The routine procedure consisted in the removal and examination of the orbital contents in a darkened room to detect red-fluorescent glands or tissues. More specific details of the apparatus, conditions, and technic of such examinations have been described previously (16, 18).

The following animals were examined: 1,245 mice, 368 rats, 20 guinea pigs, 18 rabbits, 15 cats, 12 dogs, 12 chickens, 6 bats, 6 monkeys, 5 hamsters, 4 pigs, 3 squirrels, 2 opossums, 2 turtles, 2 cows, 2 alligators, 1 raccoon, 1 fox, 1 rattlesnake. The data on the fluorescence of the orbital contents and other organs of 8 human subjects examined at necropsy have been included.

The cancer susceptibility of some of the animals was estimated from a summarized tabulation of the data in Hartwell's survey of compounds (25) that have been tested for carcinogenic activity (Table II). The data that did not state the definite number of animals treated or the number of tumors induced were excluded. The table was then used to compare the harderian gland fluorescence with cancer susceptibility. Andervont's data on latent periods of induced tumors in mice, which were summarized by Fieser (14), were also used to estimate susceptibility in a few strains of mice, and the data of Burdette and
The white fluorescence of the clitoris. An exudate that was slightly white-fluorescent was often seen on the clitoris. Tables IV and V offer a more complete summary of most of those cases showing large amounts of red-fluorescent material on the labia, vagina, or cervix.

Table III lists the cases by principal diagnosis. They have been arbitrarily fitted into 17 diagnoses, each

**Table III: General Summary of Red Fluorescence on Genitalia of Women**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Normal</th>
<th>Carcinoma of Cervix</th>
<th>Carcinoma of Clitoris</th>
<th>Pulmonary Tuberculosis</th>
<th>Acute Cervicitis</th>
<th>Chronic Cervicitis</th>
<th>Pregnancy</th>
<th>Incomplete Abortion</th>
<th>Syphilis, Recent</th>
<th>Hyperthyroidism, Pronounced</th>
<th>Fibromyomas</th>
<th>Abortion of Cervix, Recent</th>
<th>Metrorrhagia, Unknown Etiology</th>
<th>Atrophy of Vulva or Vagina and Cervix, Pronounced</th>
<th>Miscellaneous</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td>1</td>
<td></td>
<td>31</td>
<td>40</td>
</tr>
</tbody>
</table>

a) Being given 1. Carcinoma cases have already been discussed; some of the untreated ones are given in detail in Table V. There were 7 cases of acute cervicitis. The smears from 3 of these were positive on gram stain for gonococci. In 1, the cervix was hypertrophied, eroded, and appeared granulomatous. Stain for gonorrhea, dark field examination, and serological tests were negative. Repeated biopsies showed acute and chronic inflammatory reaction without any evidence of malignancy. All these cases were accompanied by a purulent discharge, which was not red-fluorescent. About 35 women showed chronic infection of the cervix, but all except 5 could be placed under another diagnosis; the cervix of none of these 5 women was red-fluorescent. One of these was cauterized after the initial examination; inspection 2 weeks later failed to show any evidence of red fluorescence.

Ten pregnant women were examined. All the trimesters were represented; 2 were in labor, in 1 of whom the membranes had ruptured before examination; the other had her membranes intact and the mucous plug was nonfluorescent. No red fluorescence was seen on any of these women except for moderate red fluorescence on the clitoris in the 2 women in labor. Two patients were seen bleeding slightly after an incomplete abortion. One of these showed red fluorescence of the cervix that was not present on examination 1 week later.

Two women had recently acquired syphilis, 1 with a freshly healed primary chancre on the labia minora, the other with a condyloma latum on the left labia minora. The latter lesion measured about 4 cm. in diameter and contained spirochetes. Neither patient showed fluorescence of the labia, vagina, or cervix.

Four women had fibromyomas of the uterus large enough so that they could be diagnosed with certainty on examination. Only 1 of these showed notable red fluorescence of the vagina, cervix, and labia. Two

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*Permission to reproduce this illustration, which was previously published (17) in the Journal of Laboratory and Clinical Medicine (C. V. Mosby Co.), is gratefully acknowledged.*
Strong (6) were employed to indicate the susceptibility of mice of C3H and JK strains.

RESULTS

Red-fluorescent porphyrin-excreting glands were found in the orbital cavities of all rats, all young mice, and some old mice. Derrien and Turchini (10) had described the red fluorescence of the harderian gland in these rodents of the genus Mus as early as 1924. Well-developed harderian glands were found in rabbits and guinea pigs but these were white-fluorescent or pale tan-fluorescent. The lacrimal glands and orbital tissues of the various other reptiles, birds, and mammals mentioned above were not red-fluorescent.

The most intense red fluorescence of the harderian gland was seen in the rat. In the hamsters, another red fluorescence at variable ages (between 200 and 300 days), while this persisted in the mice of the

rodent though not a member of the same genus as mice and rats, red-fluorescent harderian glands were also observed. It was evident that the intensity of the red fluorescence was less than in the rat, and approximately equal to that found in the susceptible C3H mouse.

The red fluorescence of the harderian gland of mice of several strains has been described previously (18). The observations in this series were limited to mice of the C3H, A, JK, I, and C57 strains, which were the progeny of mice obtained from the colony of L. C. Strong. The harderian glands of immature mice from all strains were not red-fluorescent. The harderian glands from all strains developed red fluorescence at about the time the mice matured. The glands from mice of the C3H strain showed the maximum intensity and from C57 the least intense red fluorescence, while those from mice of the other strains exhibited intermediate red fluorescence (Table I). In the mice of certain strains (C57, JK, and I) the glands lost the red fluorescence at variable ages (between 200 and 300 days), while this persisted in the mice of the

The table also shows that they are the animals of choice for testing carcinogenic chemicals, probably because of their high susceptibility. Hamsters have not been used extensively, but the data in the table indicate that they are as susceptible as mice to methylcholanthrene tumors. This extreme susceptibility of the hamster was observed by Gye and Foulds.

TABLE I: HARDERIAN GLAND FLUORESCENCE AND SUSCEPTIBILITY TO Methylcholanthrene Induced Tumors

<table>
<thead>
<tr>
<th>Strain</th>
<th>Young mice</th>
<th>Old mice</th>
<th>Average intensity of red fluorescence of harderian gland</th>
<th>Latent period in weeks, MCA induced tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3H</td>
<td>+++++++</td>
<td>+</td>
<td>8.5</td>
<td>9.6</td>
</tr>
<tr>
<td>A</td>
<td>+++++</td>
<td>++</td>
<td>10.5</td>
<td>14.0</td>
</tr>
<tr>
<td>I</td>
<td>++</td>
<td>+</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>JK</td>
<td>+</td>
<td></td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>C57</td>
<td>+</td>
<td></td>
<td>19.9</td>
<td></td>
</tr>
</tbody>
</table>

* Andervont's data from Fieser's review.
† Burdette and Strong's data.

TABLE II: THE COMPARATIVE SUSCEPTIBILITY OF ANIMALS TO THREE POTENT CARCINOGENIC HYDROCARBONS

<table>
<thead>
<tr>
<th>Animal</th>
<th>1,2,5,6-Dibenzanthraene</th>
<th>3,4-Benzpyrene</th>
<th>20-Methylcholanthrene</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number treated</td>
<td>Number tumors</td>
<td>Per cent</td>
<td>Number treated</td>
<td>Number tumors</td>
</tr>
<tr>
<td>Mouse</td>
<td>11,594</td>
<td>4,553</td>
<td>39.3</td>
<td>6,020</td>
</tr>
<tr>
<td>Rat</td>
<td>1,412</td>
<td>314</td>
<td>22.2</td>
<td>2,991</td>
</tr>
<tr>
<td>Rabbit</td>
<td>265</td>
<td>20</td>
<td>7.5</td>
<td>238</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>25</td>
<td>2</td>
<td>8.0</td>
<td>52</td>
</tr>
<tr>
<td>Fowl</td>
<td>234</td>
<td>57</td>
<td>24.3</td>
<td>50</td>
</tr>
<tr>
<td>Hamster</td>
<td>18</td>
<td>0</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Newt</td>
<td>214</td>
<td>0</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Frog</td>
<td>6</td>
<td>0</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Ferret</td>
<td>6</td>
<td>0</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Dog</td>
<td>0</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Monkey</td>
<td>22</td>
<td>0</td>
<td></td>
<td>22</td>
</tr>
</tbody>
</table>

* It should not be inferred from the data in this table that the human subject is resistant to carcinogenic agents. The 22 subjects tabulated were all patients with cancer. The benzpyrene was applied in these cases to treat the cancer and not to induce cancer. Two tumors have been recorded in laboratory workers who handled benzpyrene and methylcholanthrene, respectively. Other investigators deliberately painted 26 patients with benzpyrene daily for periods up to 120 days. The "precancerous changes" that developed regressed within 2 months after the cessation of treatment. (See Cook, J. W., and Kennaway, E. L., Am. J. Cancer, vol. 39, 1940, for original references.)
(22) and also by Halberstaedter (24). The consideration of their data stimulated the examination of the hamster. The hardier gland of the hamster was found to be red-fluorescent, hence it may be stated that the three animal species that have been found most susceptible to chemical carcinogens all have red-fluorescent, porphyrin-excreting hardier glands.

Table II indicates that mammals other than rodents have not been frequently selected to test carcinogenic hydrocarbons. The table is probably misleading in this respect, because many of the experiments that gave negative results were probably not reported. Cats and monkeys are not even mentioned, but monkeys have undoubtedly been given massive doses of one or all these three compounds (1).

Susceptibility to the production of experimental neoplasia by ultraviolet irradiation has been reviewed by Blum (4), who states that mice and rats are the only animals that have responded with tumors. Rabbits and guinea pigs, whose hardier glands are not red-fluorescent, are refractory. Even prolonged irradiation of rabbits did not induce tumors (32), whereas the same investigators readily produced tumors in A and C strain albino mice. As C57 mice required more irradiation these data show that the animals most susceptible to the induction of tumors by light had red-fluorescent hardier glands.

Various factors such as pigmentation or thickness of the hair or epidermis have been advanced (4, 26, 27, 28) to account for the observed differences in susceptibility and the sites of development of tumors. These are all logical suggestions and the influence of these factors cannot be denied. However, a study of the porphyrin metabolism of the rat and the ultimate fate of the porphyrin secreted by the hardier gland (Plate I) shows that these porphyrins could be potent factors in determining the sites where tumors develop in rodents irradiated with ultraviolet light. Most investigators have observed that ultraviolet light induces malignant transformations on the ears, nose, forepaws, and about the eyes (3, 4, 26, 27, 28, 31); even depilated areas do not respond so readily as these sites. It may be seen (Plate I) that the areas where porphyrins from the hardier gland have a tendency to accumulate on the skin are precisely those that develop tumors when these animals are irradiated. According to Roffo (31), the forepaws of rats frequently develop tumors. The hair, pigment, and epidermal thickness are essentially the same on forepaws and hindpaws, but the forepaws (Plate I) are exposed to much more porphyrin from the hardier glands because they are used to wash the face with saliva and they thereby spread the porphyrins from the mouth and nose to the ears and other parts of the head.

The porphyrin-encrusted animal in the illustration had been fed a diet deficient in pantothenic acid (17). This caused changes in water metabolism (15) and decreased the production of saliva, so that the excreted porphyrin accumulated and became more abundant on the nose; in the normal rat this would have been smeared about on the ears and head. There is actually much more porphyrin on the ears and head of the vitamin-deficient rat than appears in the fluorescence photograph, because the intense blue-white fluorescence of thick fur dominates the picture except where the porphyrins are most abundant. This is also true of the normal rat, hence it is only occasionally that porphyrins become so abundant on the ears, nose, and forepaws as to fluoresce intensely enough to predominate over the fluorescence of the fur in these regions. For this reason the photograph of the vitamin-deficient rat, in which there was admittedly an exaggeration of the normal condition, was used to illustrate this point. Porphyrin encrustations on the nose have also been produced by water deprivation (15). Even the small amounts observed on the ears, eyes, nose, and forepaws of normal animals may be sufficient to sensitize the cells in these areas to the carcinogenic action of ultraviolet light and determine the site of neoplasia.

A subsidiary experiment was performed to determine the fate of porphyrin injected into mice and rats. It was found that when these animals were injected with hematoporphyrin or protoporphyrin 9, these substances accumulated in the skin and subcutaneous tissues so that the entire shaved animal fluoresced red. In the injected unshaved animals only the skin of the ears, nose, eyelids, feet, and tail were red-fluorescent. With the exception of the hind feet, these are the areas most susceptible to the induction of tumors with light. Injected porphyrins also increased the intensity of red fluorescence of the hardier gland. These experiments demonstrate that if porphyrins were produced in excess in any tissue or organ of the rat they would become abundant in the skin, subcutaneous tissues, and hardier gland. Furthermore, the fact that these substances fluoresced when the animal was irradiated with near ultraviolet light indicates that they accumulated at depths that were reached by the wave lengths that incite fluorescence. Two possibilities, therefore, exist with regard to the site of action of the porphyrins that appear to sensitize mice and rats to light carcinogenesis: (a) sensitization may be due to the presence of porphyrins smeared on externally as the result of spreading hardier gland secretion, or (b) the sensitization may be related to the synthesis or accumulation of porphyrins in the skin and subcutaneous tissues of these rodents.
DISCUSSION

On the basis of red fluorescence alone Körbler (30) stated that "hematoporphyrin," acting as a photo-dynamic sensitizer, was an etiological factor in the production of cancer of the skin in the human subject. This view developed from an analysis of data ascribed to hematoporphyrin because this porphyrin is excreted in the urine of mice. Mice and rats would not be appropriate animals to use for testing the sensitizing influence of hematoporphyrin (40) observed no conclusive influence on the basis of hematoporphyrin sensitization has been justly and unjustly criticised by several investigators (4, 28).

The criticism that red fluorescence is not a satisfactory proof of hematoporphyrin (28) is valid for any porphyrin. This hypothesis, which resembles the one that has been developed in this work, is extremely interesting, but it is unfortunate that the red fluorescence was ascribed to hematoporphyrin because this porphyrin forms only under artificial conditions (11, 21).

Hematoporphyrin has also been used to enhance tumor formation in mice by light (5), but other investigators (40) observed no conclusive influence on the rate of induction of benzpyrene tumors in irradiated mice. Mice and rats would not be appropriate animals to use for testing the sensitizing influence of porphyrins or other sensitizing agents because these animals manufacture and excrete excess porphyrins. In this connection it is of interest that the administration of 1,2,5,6-dibenzanthracene to rabbits results in urinary excretion of abnormal amounts of coproporphyrin I (11). Coproporphyrin I and protoporphyrin 9 have little photosensitizing action (21) as compared with hematoporphyrin. However, one or both of the former may be more potent in sensitizing cells to the carcinogenic influence of light or chemical carcinogens.

The constant and simultaneous occurrence of pairs of porphyrins was referred to by Fischer (21) as the dualism of the porphyrins. It is generally assumed that this dualism is the result of a necessarily mixed synthesis. Coproporphyrin I according to this concept is a coincidental, nonfunctional by-product of protoporphyrin synthesis. It may well be that coproporphyrin I does have some function to perform. Either coproporphyrin I alone or the ratio of protoporphyrin 9 and coproporphyrin I may regulate the mechanisms that initiate cell division and growth. For a more extensive discussion of the normal occurrence, abundance, and fate of these two porphyrins in living tissues than that which follows, the reader is referred to comprehensive reviews (11, 21, 34, 41, 43) in which the original references have been given.

Metal porphyrin protein complexes such as hemoglobin, chlorophyl, myoglobin, cytochrome c, catalase, and peroxidase occur in practically all cells. Free protoporphyrin 9 and coproporphyrin I are, however, not so abundant in most cells, though commonly found in young tissues and in cells undergoing rapid division. In vertebrates in general, and mammals and man in particular, there is a considerable body of evidence to support the view that protoporphyrin 9 and coproporphyrin I are formed as intermediates in the synthesis of hemoglobin (11, 21, 34). However, these substances are not formed in the normal degradation of hemoglobin (11, 34). If the other iron porphyrin substances (myoglobin, cytochrome c, etc.) normally found in many cells undergo similar degradation, the intermediate decomposition products are not known. Porphyrins may be formed in this process, but even so the amount from this source would be relatively small.

The most striking example of the association of high concentrations of protoporphyrin 9 and coproporphyrin I with the tissues and cells that are actively growing and dividing is found in the bone marrow (34). Here the rate of cell division is higher throughout life than in any other organ or tissue in the body. Amniotic fluid, developing embryos, and chick embryos contain protoporphyrin in relatively large amounts (34). Other areas where porphyrins and rapid mitosis occur coincidently are the base of hair follicles, the skin, growing cartilage, and ossifying tissues (20). Rapidly growing organisms such as yeasts and bacteria produce relatively large quantities of protoporphyrin 9 and coproporphyrin I (21).

The porphyrins present in tissues that are actively growing and dividing are probably synthesized within the cells. The association of protoporphyrin 9 and dividing cells may be coincidental and depend upon the necessity of supplying the newly formed cells with the required complement of iron-porphyrin enzymes that are not later replaced or, if so, only slowly. The rapid synthesis of porphyrin in the cell would thus not occur until cells prepare to undergo division. On the other hand, protoporphyrin 9 and coproporphyrin I synthesis may be speeded up in the cell in an attempt to compensate for an inadequate metabolic mechanism. The inadequate metabolic mechanism postulated as a primary stimulus to porphyrin formation may be the result of (a) changes in the size of the cells that disturb the normal ratio of cell surface and volume; (b) the destruction, inactivation, or deficiency of heme or non-heme respiratory enzymes; (c) an intracellular parasite such as a virus that may require the protein or heme component...
of a respiratory enzyme such as cytochrome c for its continued existence. With reference to the second and third possibilities just stated, a deficiency of cytochrome c (12) and other cytochromes (38) has been demonstrated in various malignant tissues. There are numerous other mechanisms that might interfere with the cellular metabolism and cause increased production or accumulation of protoporphyrin 9 and coproporphyrin I. According to the hypothesis, these excess porphyrins would then sensitize the cells to the action of normal as well as abnormal growth-stimulating factors or relatively weak carcinogenic agents.

SUMMARY

(a) The examination of numerous birds, reptiles, and mammals showed that red-fluorescent harderian glands were present only in mice, rats, and hamsters. The data in the literature indicate that of all the animals tested, these three species are the most susceptible to induction of tumors by carcinogenic agents. Since the red-fluorescent porphyrin-excreting harderian gland reflects the porphyrin metabolism of other organs and tissues, a relationship between excess porphyrins (or a unique porphyrin metabolism) and susceptibility to carcinogenic agents is postulated. Protoporphyrin 9 and coproporphyrin I are the specific porphyrins excreted by the harderian glands.

(b) When porphyrins were injected into the peritoneal cavity of rats, these substances soon became concentrated in the skin and subcutaneous tissues and the harderian glands. A study of the ultimate fate of the porphyrins excreted by the harderian glands shows that they are smeared on the areas of the skin of mice and rats where tumors develop when these animals are irradiated with ultraviolet light. Here, too, the only animals that have been found susceptible to the induction of tumors by ultraviolet light are mice and rats, which have red-fluorescent (porphyrin-excreting) harderian glands. These data support the original hypothesis that there is a direct or an indirect relationship between porphyrins or porphyrin metabolism and cancer susceptibility.

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