Comparative Glycolytic and Respiratory Metabolism of Homologous Normal, Benign, and Malignant Rabbit Tissues

With Particular Reference to the Benign Virus Papilloma (Shope) and a Transplanted Cancer Derived Therefrom (the V2 Carcinoma)

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(Received for publication December 30, 1943)

To learn more about the changes that take place when benign tumor cells become malignant, and whether the malignant cells possess an altered metabolism, we have undertaken a comparative study of certain rabbit tumors and tissues of homologous sorts. Special attention has been given to the benign epidermal papillomas caused by the Shope virus (24), and to the V2 carcinoma—a squamous cell cancer derived originally from the cells of a Shope virus papilloma, and maintained for several years by transplantation (15). Normal and hyperplastic skin have also been studied, as well as autochthonous squamous cell carcinomas originating in virus papillomas (19), and a second transplanted epidermoid cancer—the Brown-Pearce carcinoma, which arose at the site of an old syphilitic lesion (3, 17). In addition to these epidermoid tissues, the observations have been extended to a virus-induced fibroma (23), and to a transplanted sarcoma (sarcoma I of Andrewes and Ahlström) that arose in voluntary muscle where tar and the fibroma virus had both been present (1). Values for anaerobic and aerobic glycolysis, respiratory quotient, oxygen consumption, and certain derived quotients were determined in glucose-bicarbonate medium by standard methods (8), and for oxygen consumption response to added succinate and para-phenylenediamine (9, 18, 22) when the tissues were in glucose-phosphate medium.

As bearing upon the interpretation of the metabolic findings, particular attention has been given to a histologic analysis of the materials actually employed in the manometric experiments. Sections were made of the tissue slices after the metabolic measurements had been made on them, as well as of representative slices taken before measurement. Though the tissues were all carefully selected, microscopic examination showed that cells of the types sought for study often made up only half or less of the bulk of the slices put into the Warburg vessels. For example, normal skin, and skin rendered hyperplastic by 3 or 4 applications of turpentine-acetone mixture (11), when carefully shaved from a stretched surface in a layer about 0.1 mm. thick, still provided slices that contained only a small proportion of epidermal cells (5 to 25 per cent), the rest being derma that could not feasibly be trimmed away. The “healthiest” parts of the primary carcinoma likewise contained only a rather small proportion of neoplastic cells, edematous stroma comprising the bulk; and slices of these primary tumors were, in addition, usually pultaceous in spots from bacterial infection. The benign virus papilloma and the transplanted V2 carcinoma, on the other hand, provided much more suitable materials. By taking only the basal portion of young, vigorously proliferating papillomas, slices could be procured that contained about 70 to 80 per cent or more of living papilloma cells, along with some 25 to 15 per cent or less of keratinized papilloma cells and a small proportion of derma. Furthermore, the metabolism of the keratinized cells as such could be studied by slicing separately the upper half of papillomas 4 to 6 mm. high; such slices contained about 90 per cent or more of dead squames and 10 per cent or less of living papilloma cells. The V2 carcinoma provided slices composed at best of some 40 to 60 per cent of “healthy” carcinoma cells, the rest being edematous stroma containing immature fibrocytes and occasionally infiltrated with wandering cells, chiefly lymphocytes. To evaluate the metabolism of this stroma, slices were selected for test that were composed mainly of it, with only some 15

* With the technical assistance of Marie L. Hesselbach and Doris F. MacNeary.
to 30 per cent of carcinoma cells. Additional studies were made with the benign virus-induced fibroma, which, though quite different in microscopic appearance from the V2 stroma, is also an edematous tissue containing proliferating fibroblasts that often appear "sick"; it regularly regresses (23), and is not neoplastic in a strict sense.

EXPERIMENTAL RESULTS

Metabolism of malignant, benign, and normal rabbit tissues in bicarbonate medium.—Table I provides a summary of the glycolytic and respiratory estimations. The V2 carcinoma slices having 40 to 60 per cent of malignant cells yielded by our technic anaerobic glycolysis values (Q\textsubscript{NA}) averaging 10.2, and aerobic glycolysis values (Q\textsubscript{OA}) averaging 4.6. The Q\textsubscript{NA} values for the Brown-Pearce carcinoma (average 11.8) were slightly greater than those for the V2 carcinoma, and so, too, were those for the rabbit sarcoma I of Andrews and Ahlström (average 12.0). The average Q\textsubscript{NA} value obtained with V2 carcinoma slices containing a preponderance of stroma was relatively low (6.3), and that for the virus-induced fibromas was notably so (2.9).

The papilloma slices having 70 to 85 per cent of living cells gave average anaerobic and aerobic glycolysis values of 6.9 and 2.8 respectively. These values, it will be observed, are significantly lower than the corresponding average values for the V2 carcinoma, as statistical analysis confirms. It is noteworthy, moreover, that the papilloma slices contained a greater percentage of neoplastic cells than did the V2 carcinoma slices (second column of Table I) and that the observed differences in the metabolism of the two tissues become even greater if allowance is made for this factor. In this connection, the benign papilloma of the wild cottontail rabbit gave metabolic values indistinguishable from those of the domestic rabbit growth, whereas the keratinized papilloma, which provided slices containing 10 per cent or less of living cells, gave negligible Q\textsubscript{NA} values.

The findings with the skin and primary carcinoma tissues are included, but owing to the small proportion of epidermal cells present in the slices and to the bacterial infection of the carcinomas it is difficult to make a close quantitative comparison between these tissues and the Shope virus papilloma or the transplanted malignant tumors. It will be noted that the skin slices provided Q\textsubscript{NA} and Q\textsubscript{OA} values considerably lower than those for the papilloma slices, but the differences may have been due to the much lower proportion of epidermal cells present in them. In this connection, Berenblum, Chain, and Heatley (2), who used a special technic for slicing and nucleic acid-phosphorus content instead of dry weight for comparison, reported no difference between the glycolyzing capacity of normal rabbit skin and of benign papillomas induced with the Shope virus. The cellular composition of their materials was not described, however, and hence comparisons on a basis of content of homologous epidermal cells cannot be made. It has been indicated elsewhere (6, 10) that they did not extend their studies to homologous malignant tumors, which, as our findings show, differ significantly in glycolyzing capacity from the benign papilloma.

Further information is provided by the derived metabolic quotients (Table I), which relate glycolysis to oxygen consumption independently of dry weight, although it is to be noted that certain of the quotients are calculated from comparatively few determinations. The V2 carcinoma yielded a positive fermentation excess, an extent quotient above zero, and Myerhof oxidation quotient several times unity, in which respect it may be considered characteristic of "malignancy" within the limitations of these criteria (4-6). The Shope virus papilloma cells provided a fermentation excess quotient of approximately zero, and an extent quotient of about 6.0, in addition to intermediate glycolysis rates. The quotients given by the skin slices indicate a difference between this tissue and the benign papilloma that is not brought out by a consideration of the glycolysis values alone. In our experiments the Myerhof oxidation quotient for skin was less than unity, the fermentation excess was negative, and the extent quotient was only half as great as that for the papilloma. Values for the two latter quotients that similarly differentiate the normal skin and the benign papilloma may be calculated from the data of Berenblum, Chain, and Heatley already mentioned, even though their values for anaerobic glycolysis failed to distinguish between the two tissues. In passing it is interesting to note that the extent quotient for the virus-induced fibroma is very high (14.5), suggestive of "malignancy," but its low Q\textsubscript{NA} and Q\textsubscript{OA} values preclude this characterization (4-6).

The respiratory quotients of the tissues (skin, hyperplastic skin, fibroma, papilloma, and V2 carcinoma) were all below unity. Previous observations have pointed to the lack of distinction in this regard between the generality of tumors and the majority of adult tissues (4-6, 10).

It is noteworthy that the per cent dry weight of the tissues varied from 10.5 in the case of the fibroma to 24.0 in the case of normal skin, and that of the differences, notably that between the V2 carcinoma (dry weight=12.9 per cent) and the virus papilloma (dry weight=17.9 per cent), are decreased if the Q values are calculated on the basis of wet weight.
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Histological analysis of tissue slices employed</th>
<th>Per cent dry weight</th>
<th>Anaerobic glycolysis $Q^a_O^2$</th>
<th>Aerobic glycolysis $Q^a_O^4$</th>
<th>Respiratory quotient R.Q.</th>
<th>Oxygen consumption $O_2$</th>
<th>Extent quotient $M/Q$</th>
<th>Fermentation excess, U $O^2_n - 2O_n$</th>
<th>Meyerhof oxidation quotient, $M.O._Q$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted V2 carcinoma derived † from the Shope virus papilloma (15); 32nd and 34th transfers (10-20 days)</td>
<td>About 30-60% carcinoma cells; remainder edematous stroma, composed mainly of fibrocytes, usually infiltrated scantily with wandering cells, chiefly lymphocytes</td>
<td>12.9±</td>
<td>10.2±</td>
<td>4.6±</td>
<td>0.67±</td>
<td>3.2±</td>
<td>9.5</td>
<td>3.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Brown-Pearce carcinoma (20 days) (5)</td>
<td>About 65% malignant cells; remainder muscle and necrotic tumor cells, lymphocytic infiltration scanty</td>
<td>15.4±</td>
<td>11.8±</td>
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<tr>
<td>Andrews-Ahlstrom sarcoma (R.S.I.) (20 days) (1)</td>
<td>About 55% malignant cells; remainder muscle and necrotic tumor cells, lymphocytic infiltration scanty</td>
<td>14.3±</td>
<td>12.0±</td>
<td></td>
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<tr>
<td>Benign Shope virus papilloma (domestic rabbit, 3-32 wks.) (24)</td>
<td>About 70-85% living papilloma cells; 10-20% keratinized papilloma cells; remainder derma</td>
<td>17.9±</td>
<td>6.9±</td>
<td>2.8±</td>
<td>0.84±</td>
<td>3.0±</td>
<td>6.9</td>
<td>+0.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Benign Shope virus papilloma (wild cottontail rabbit, 4 wks.) (24)</td>
<td>Similar to domestic rabbit papilloma</td>
<td>19.9±</td>
<td>6.9±</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Keratinized papilloma (upper half of growths; 0.4-0.6 cm. tall)</td>
<td>0-10% living papilloma cells; remainder mostly dead squames</td>
<td>20.9±</td>
<td>0.5±</td>
<td></td>
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</tr>
<tr>
<td>V2 carcinoma as above, but selected so that bulk of tissue was stroma</td>
<td>About 15-30% V2 cells; remainder stroma</td>
<td>11.5±</td>
<td>6.3±</td>
<td></td>
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</tr>
<tr>
<td>Virus-induced fibroma (6-13 days) (23)</td>
<td>Edematous, collagenous tissue containing fibroblasts, usually infiltrated moderately with wandering cells, both polymorphonuclear leukocytes and lymphocytes</td>
<td>10.5±</td>
<td>2.9±</td>
<td>1.3±</td>
<td>0.92±</td>
<td>0.6±</td>
<td>(14.5)</td>
<td>(1.7)</td>
<td>(8)</td>
</tr>
<tr>
<td>Primary carcinomas originating in 32 wks. old Shope virus papilloma (19)</td>
<td>About 20-30% squamous carcinoma cells amidst myxomatous stroma</td>
<td>13.0±</td>
<td>5.0±</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal skin (ear, belly)</td>
<td>About 5-15% normal epidermal cells; remainder derma</td>
<td>24.0±</td>
<td>1.5±</td>
<td>1.4±</td>
<td>0.89±</td>
<td>1.0±</td>
<td>4.5</td>
<td>−0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyperplastic skin (belly, induced with acetone-turpentine) (11)</td>
<td>About 15-25% normal and proliferating epidermal cells; remainder derma</td>
<td>20.0±</td>
<td>2.3±</td>
<td>1.8±</td>
<td>0.86±</td>
<td>3.3±</td>
<td>2.1</td>
<td>−4.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Measurements made at 38° C, pH 7.4, in Warburg-Okamoto Ringer solution (0.025 M NaHCO₃); 0.2% glucose in Warburg or Summerson manometers. $Q$ values represent cmm./hr./mgn. initial (aliquot) dry weight of tissue; superscripts refer to number of manometric determinations made, subscripts to number of tumors examined. * S. E. for mean values of 10.2 and 6.9 are ±0.34 and ±0.32 respectively; P value for difference of means is less than 0.01.

† Numbers in parentheses indicate references.
Oxygen consumption response of malignant, benign, and normal rabbit tissues to succinate and paraphenylenediamine.—It will be seen from Table II that the 3 transplanted cancers (V2 carcinoma, Brown-Pearce carcinoma, and rabbit sarcoma I) yielded average $Q_o_2$ values in the presence of glucose that were increased 120 per cent at the most upon the addition of paraphenylenediamine, and less than 40 per cent by succinate. The respective increases with the benign Shope virus papilloma and the virus-induced fibroma were also similar. Tests with a number of normal domestic rabbit tissues, including embryonic liver, showed, however, that the $Q_o_2$ of these was stimulated much more by paraphenylenediamine and succinate than were the neoplastic tissues. In subsidiary experiments not reported in detail here, a series of normal adult cottontail rabbit tissues, and a series of 12 to 17 day old chick embryo tissues of the types reported in Table II for the domestic rabbit, likewise gave $Q_o_2$ values that were in general increased one to several fold by paraphenylenediamine. The greatest percentage responses usually, but not always, came from

<table>
<thead>
<tr>
<th>Domestic rabbit tissue</th>
<th>Paraphenylenediamine (1 mgm./cc.)</th>
<th>Succinate (0.02 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of determinations</td>
<td>Minus</td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V2 carcinoma</td>
<td>5 (4)</td>
<td>2.9</td>
</tr>
<tr>
<td>Brown-Pearce carcinoma</td>
<td>4 (2)</td>
<td>4.2</td>
</tr>
<tr>
<td>Andrewes-Ahlström sarcoma (RSI)</td>
<td>3 (2)</td>
<td>3.8</td>
</tr>
<tr>
<td>Benign Shope virus papilloma (3-32 wks.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Wild cottontail rabbit)</td>
<td>16 (11)</td>
<td>2.4</td>
</tr>
<tr>
<td>Virus-induced fibroma (Shope) §</td>
<td>7 (5)</td>
<td>2.3</td>
</tr>
<tr>
<td>Keratinized papilloma (90-100% maturated squares; remainder living pap. cells)</td>
<td>6 (3)</td>
<td>1.2</td>
</tr>
<tr>
<td>V2 &quot;stroma&quot; (70-85% nonneoplastic stroma; remainder V2 carcinoma cells)</td>
<td>9 (4)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Normal

Spleen

Lung

Skin

Embryonic liver (17 days)

Pancreas

Kidney cortex

Kidney medulla

Brain

Retina

Ovary

Adult liver

Voluntary muscle (leg)

Adrenal gland

Heart muscle

Diaphragm fascia

Diaphragm muscle

$Q_o_2$ = cmm. O$_2$ consumed/mgm. initial aliquot dry weight/hr. "Minus" and "plus" $Q_o_2$ values are averages of individual determinations based on readings taken for respectively 1 hour before and 1 to 1 hour after adding succinate or paraphenylenediamine from vessel side arm to a given tissue slice sample. Thus a given sample served to give a plus as well as minus value. The average increases and percentage increases in $Q_o_2$ due to succinate and paraphenylenediamine have been calculated from averages of such individual determinations, not from the difference in the average minus and plus values reported.

* Values in parentheses refer to number of tumors studied.
yses between the sixth and 14th weeks following virus inoculation. Their first 2 specimens (at 6 and 7 weeks) were described as "pre-papillomatous" lesions, and they yielded QO2 values in glucose phosphate of 1.07 and 0.28, respectively, which were increased two to fourfold upon addition of succinate or paraphenylenediamine. The subsequent specimens, procured 10 and 14 weeks after virus inoculation, were histologically benign papillomas of characteristic sort, and they gave QO2 values of 3.0 and 3.2 (average of two determinations) respectively, which were not increased upon addition of either of the substrates. In a subsequent paper (18), they report further observations on tissues procured after 46, 55, and 79 weeks; the first two of these specimens were benign papillomas while the last (79th week) was carcinomatous. All three materials yielded QO2 values (averaging around 4.3) that were not notably increased by paraphenylenediamine and succinate. From these observations, Salter and his colleagues have concluded that in the benign papilloma "... a loss of cytochrome system response occurred rather abruptly after several weeks, and before histological evidence of frank malignancy was present" (9).

While our findings agree in general with those of Salter and his colleagues, in that the normal tissues studied (including embryonic ones) usually gave a greater oxygen consumption response to added paraphenylenediamine and to succinate than did neoplastic tissues of homologous sorts, still they differ notably in one important particular: There was no significant difference in the QO2 response of young and old papillomas to the added substrates. Determinations were made on papillomas from 9 rabbits 3 to 4 weeks after virus inoculation when the growths were raised 1 to 3 mm. above the surrounding skin—the earliest stage at which any considerable mass of papilloma tissue is available for slicing—and on the papillomas from 5 rabbits 11 to 32 weeks after virus inoculation (when the growths were raised 6 to 12 mm.). The average QO2 value for the younger papillomas was 2.2 (range, 1.4 to 3.1), and this was increased 56 per cent (range, 10 to 135) by paraphenylenediamine, and 14 per cent (range, 21 to 51) by succinate. The older growths also gave an average QO2 value of 2.2 (range, 1.9 to 3.4), which was increased 81 per cent (range, 18 to 112) by paraphenylenediamine and 51 per cent (range, 36 to 65) by succinate. It seems plain that the benign virus papillomas produced in domestic rabbits give, from a very early state, low QO2 responses to added paraphenylenediamine or succinate, and that they do not differ in this respect from the homologous malignant V2 carcinoma derived from the papilloma. As bearing further on the low QO2 responses of tissues to the added substrates as a measure of their benign or malignant character, the fact deserves mention that the virus papillomas in wild cottontail rabbits, which only rarely become malignant (13), gave no greater QO2 responses to the added substrates (Table II) than did the domestic rabbit papillomas, which usually become cancerous, though after many months' growth (20, 21).

It should be pointed out also that our keratinized papilloma slices, which contained 90 to 100 per cent of maturated squames and 10 per cent or less of living papilloma cells, yielded QO2 values averaging 0.4 that were increased 154 per cent by paraphenylenediamine, proving similar in these respects to the 6 and 7 weeks' "pre-papillomatous lesions" of Salter and his group (9, 18), and conforming in general to the pattern of the normal tissues. Much the same proved true of the V2 carcinoma slices that contained a preponderance of stroma, these yielding QO2 values averaging 2.5 that were stimulated 191 per cent (average) by the paraphenylenediamine. The virus-induced fibroma, on the other hand, which is not strictly neoplastic (23), provided slices that gave QO2 values averaging 1.2, which were increased less than 100 per cent by paraphenylenediamine and were like the generality of tumor tissues in this respect.

Warren has recently observed (25) that normal rabbit bone marrow and normal rabbit and rat kidney gave QO2 responses that were increased less than 100 per cent by added paraphenylenediamine and succinate. The kidney QO2 values in the absence of stimulator were so great (6 to 12 as privately communicated by Dr. Warren), however, that no larger percentage response could be expected, since, as Warburg's diffusion formula indicates, tissue slices can scarcely exceed QO2 values of 10 to 15 under customary technical conditions (1 atmosphere O2, slices a few tenths of a millimeter thick, etc.). The high percentage stimulation of the rabbit kidney reported in Table II was obtained with specimens whose QO2 was well below 6, whereas a specimen of wild rabbit kidney with a QO2 of 11 was observed to give a stimulation of only 29 per cent. The various findings just discussed would seem to illustrate some of the limitations of the QO2 response of tissues to added paraphenylenediamine and succinate as a criterion in the diagnosis and study of neoplasms as distinct from normal and pathologically altered, nonneoplastic tissues.

Incidental observations.—Polarographic determinations of blood proteose (27) gave average values as follows, in arbitrary galvanometer deflection units. Twenty-one normal rabbits, 1.0 (range, 0.5 to 2); 3 rabbits with Shope papilloma virus of 3 weeks' duration, 1.0 (range, 1.0 to 1.0); 10 rabbits bearing...
Shope papillomas of 10 to 32 weeks' duration, 2.0 (range, 1.0 to 3.0); 19 rabbits bearing V2 carcinomas of 10 days' to 10 weeks' duration, 4.4 (range, 3 to 8, the animals having older and larger growths in general giving the higher values); and 5 rabbits bearing Brown-Pearce carcinomas of 3 weeks' duration, 2.6 (range, 2 to 4). These findings are being considered elsewhere (27), along with a discussion of blood protease values in relation to the problem of malignancy.

A large number of biotin and miotin (7) analyses were made by yeast bioassay of representative samples of the rabbit skin, hyperplastic skin, Shope virus papilloma, and V2 carcinoma materials used for metabolism studies. The skin materials contained an average of 0.08 microgram of biotin per gram dry weight (7 determinations), the values being similar to those reported by West and Woglom (26), who used Rhizobium rather than yeast as the bioassay organism. The papillomas and carcinomas gave the same average values for total biotin of about 0.13 microgram per gram dry weight (15 determinations each), West and Woglom having reported values of about 0.36 microgram for both materials. The miotin content of the V2 carcinomas ranged from 10 to 33 per cent of the total biotin, whereas that of the papillomas ranged from 6 to 15 per cent, and that of the skin from 2 to 9 per cent. A great variety of normal tissues from different species have yielded miotin values (7) of about 1 to 5 per cent of the total (range, 0.1 to 10 per cent). The comparatively high miotin content of the V2 carcinoma suggests that an altered biotin metabolism may be involved in the cells of this growth, but this remains problematical.

**SUMMARY AND COMMENT**

Data have been procured that indicate that the cells of the V2 rabbit carcinoma possess a glycolyzing capacity which, calculated on a dry weight basis, is about as great as that of the cells of 2 other transplanted rabbit cancers (the Brown-Pearce carcinoma and sarcoma I of Andrewes and Ahlström), and considerably greater than that of the benign virus papilloma cells of the sort from which they originally derived. The derived metabolic quotients, which relate glycolysis to oxygen consumption independently of dry weight, lend further support to the view that the metabolism of the V2 carcinoma cells is characteristic of malignant cells generally (4-6), whereas that of the Shope virus papilloma is characteristic of benign tumor cells and distinguishable in certain respects from that of normal rabbit skin cells. The differences in metabolism between the benign papilloma cells and the homologous V2 carcinoma cells are the more noteworthy since the former proliferate quite as rapidly as the latter. It remains to be ascertained whether the metabolic differences have something to do with the differences in the form and behavior of the papilloma and carcinoma cells, with the failure of repeated attempts to procure a causative virus from the V2 carcinoma (15), or with antigenic differences in the sedimentable constituents of the two sorts of cells (14-16).

Observations were also made on the oxygen consumption (QO₂) of certain normal and neoplastic rabbit tissues in glucose-phosphate medium with and without added paraphenylenediamine and succinate. The findings in general confirm the observations of others that normal tissues as a class give greater QO₂ responses to the added substrates than do neoplastic tissues. The benign Shope virus papilloma, however, gave much the same low QO₂ responses to the added substrates as did the homologous malignant V2 carcinoma, and this proved true also of the virus-induced fibroma, which is not actually neoplastic. Certain implications of the findings are discussed.

Polarographic determinations showed that rabbits carrying V2 carcinomas had greater amounts of protease in their blood than had rabbits with Shope papillomas of 3 weeks' duration or normal controls. There was no noteworthy difference in the biotin content of the benign papilloma and the malignant V2 carcinoma, as determined by yeast bioassay, though both types of tissues contained more biotin than did normal rabbit skin. The proportion of avidin-uncombinable biotin (miotin) was exceptionally high in the V2 carcinoma. The implications of these incidental observations will be considered elsewhere.

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Cancer Res 1944;4:547-553.

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