The Age of the Tumor-bearing Hosts as a Factor Conditioning the Transmissibility of the Rous Sarcoma by Filtrates and Cells

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Fundamentally, the present paper is concerned with both the state of the Rous sarcoma virus—masked or free—when the tumor is made to grow either in old or in young hosts, as well as with properties of the tumor itself, associated with the virus in either state.

It is well known that the causative viruses of chicken sarcoma can vanish in the most unpredictable way, so that filtrates from apparently typical tumors become absolutely and persistently negative. The best example is that of Gye and Andrewes (14), who failed to show active virus in filtrates and desiccates of the Rous sarcoma in nine successive cell passages. Among studies concerning the conditions governing this phenomenon are the findings of Doerr et al. (7) and of Carr (6), showing that the activity of filtrates of the Rous sarcoma decreases to complete inactivity as the tumors grow older. The influence of the age of the host was reinvestigated by one of us (10) in a study of fourteen spontaneous chicken sarcomas in which only one out of four tumors occurring in hosts 12–18 months old was transmissible by cells and filtrates, whereas at least four out of ten tumors occurring in younger hosts were transmissible by the same preparations.

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The experimental material of this paper has been included in a dissertation presented by the junior author to the Faculty of Yale University School of Medicine, in partial fulfillment of the requirements for the degree of Doctor of Public Health.

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In this paper the terms “filtrability” and “nonfiltrability” will be used for convenience and not to indicate that the inactivity of the filtrates is due to the incapacity of the virus to pass through filters. The same fluctuations in activity have been observed with tumor preparations in which the cells have been eliminated or killed by means other than filtration (see Carr [6] and Missurski et al. [18]).

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MATERIALS AND METHODS

The animals studied were 44 adult chickens and 38 chicks, of the Plymouth Rock breed which were at an average age of 15.4 months and 15.0 days, respectively. These birds are designated “original hosts,” and their tumors “original tumors.” The Rous sarcoma was maintained by cell passages through chicks. Of the 82 tumors studied, 48 were induced by filtrates and 34 by cell suspensions. Both materials were injected into the breast in varying amounts, but the effects of variation in the amount of inoculum is not a factor in the present investigation. Chickens of the two age groups were inoculated at the same time with the same or comparable tumor materials.

The birds were killed at different intervals so as to provide tumors of different ages, and representative portions of the growths were secured for processing and for histological study.

From each tumor a cell suspension was prepared with 1 part of minced tumor tissue plus 4 of saline, and 0.1 cc. of the material was injected subcutaneously in each side of the breast of four chicks. Filtrates were prepared by grinding 1 part of tumor with sand and 19 volumes of saline, centrifuging the mixture, and passing the supernatant fluid through Berkefeld N candles. The filtrates were further diluted with saline, so that dilutions at 1:20, 1:200, 1:2,000, and 1:20,000 were obtained. Each filtrate was inoculated into six or more chicks, each of which was given an intradermal injection, in both sides of the breast and the outer side of the thighs, of 0.5 cc. of each of the four different dilutions. The sites of inoculation of each of the dilutions were shifted in different chicks.

The areas of the tumors that developed (designated as “test tumors”) were measured and recorded, generally 30 days after injection, when the birds were killed, or following natural death. In most cases the chicks developed well delimited tumors at the sites of inoculation, and whenever the growths merged with each other the results of the corresponding inoculations were discarded. Data from chicks dying within 10 days after inoculation were not included in the results. Autopsies were conducted in every case.

Transmissibility of the Tumors by Filtrates

Considering the 82 original tumors with respect to the activity or inactivity of their filtrates after inoculation into the test chicks, the results have been presented (Table 1) according to the age of the original hosts, the age of the original tumors, and the source material—cell suspensions or filtrates—by which the original tumors were induced. From these results, three main effects are

The statistical analysis of the results was carried out by one of us (P. M. Freire) and can be found in detail in his thesis for the degree of Doctor of Public Health. The authors are much indebted to Doctor C. I. Bliss for valuable help in this regard.

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DUKAN-REYNALS AND FREIRE—Age Factor on Properties of Tumor

apparent: (a) 32 out of 38 tumors (84.2 per cent) from young chickens were filtrable as against seventeen out of 44 tumors (38.6 per cent) from adult chickens; (b) as best shown in the last column of the table, an increase in the age of the tumors corresponded to a decrease in filtrability; and (c) 26 out of 34 tumors induced by cell suspensions (76.5 per cent) were filtrable, as against 23 out of 48 tumors (47.9 per cent) induced by filtrates.

Since each tumor tested was under the influence of three variables—age of the host, age of the tumor, and source material, it was necessary to evaluate the significance of each effect by a method that took into account the concomitance of these variables. It seemed appropriate to utilize the methods developed by Bliss (1-4) for the calculation of dosage-effect curves. Each group of the hosts was considered as providing two separate curves, one corresponding to original tumors induced by cell suspensions and the other corresponding to original tumors induced by filtrates. Therefore, each calculated regression line described, as an all-or-none response (positive or negative filtrates), the effect of the varying age of the original tumors.

The results of the analysis proved the statistical significance of the effects of age of the host, age of the tumor, and source material on the filtrability of the tumors, and the probabilities that the results were due to chance alone were 1 in 1,000, 1 in 170, and 1 in 500 for each of the three effects, respectively.

From this study it may be concluded: first, that the filtrability of the tumors, which is actually the presence in them of virus in a free state, is in an inverse relation to the age of the host and the age of the tumor; and, second, that free virus is more frequently present in the tumors induced by cell suspensions than in those induced by filtrates.

DEGREE OF ACTIVITY OF THE FILTRATES

We next studied whether the factors that influence filtrability as a qualitative process also influenced the degree of activity of the positive filtrates. Since there was only a rough parallelism between the areas of tumors or their logarithms and the doses of filtrate, the data were interpreted in terms of an all-or-none response—the presence of a tumor, regardless of its size, being considered as a positive response. To this effect, 50 per cent end-points were calculated by the method of Reed and Muench (19). The positive tumor filtrates were classified in three degrees of activity, according to the following median effective doses, in miligrams of tumor tissue: high titer < 0.079; intermediate titer, from 0.0079 to 7.9; low titer > 7.9.

Appropriate calculations showed that, as pointed out by a nonsignificant \( \chi^2 \) in young as well as in adult chickens, there was no association between the degree of activity of the positive filtrates and the age of the tumors. Disregarding the differences in tumor age the effects of the age of the hosts and that of filtrates or cell suspensions were evaluated: the corresponding \( \chi^2 \) analyses were again non-significant.

The above results were supplemented by data from other experiments in which 29 unaltered tumor extracts were titrated in chicks in much the same manner as described for filtrates. Each extract was prepared from pooled material from three tumors induced by cell suspension and grown for 9–16 days in chicks 12–21 days old at the moment of inoculation. The results showed that, despite the uniformity of the age of the host,

TABLE 1

FILTRABILITY OF TUMORS IN RELATION TO AGE OF THE HOSTS, AGE OF THE TUMORS, AND SOURCE MATERIAL

| AGE GROUP OF THE ORIGINAL HOSTS | AGE OF THE ORIGINAL TUMORS INDUCED BY CELL SUSPENSIONS | AGE OF THE ORIGINAL TUMORS INDUCED BY FILTRATES | ALL SOURCE MATERIALS |
|---------------------------------|-----------------------------------------------------|------------------------------------------------|--|-----------------|
| Geometric mean days of age       | Geometric mean days of age of positive filtrates | Geometric mean days of age of positive filtrates | Proportion of tumors with positive filtrates | Proportion of tumors with positive filtrates |
| <30                             | <30                                                  | <30                                              | <30                                          | <30                                          |
| >40                             | >40                                                  | >40                                              | >40                                          | >40                                          |
| All ages                        | All ages                                             | All ages                                         | All ages                                     | All ages                                     |

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age of the tumor, and source material, there was such a variation in the titers of the extracts that some of them were nearly 100 times more active than others.

In summary, the three factors that were found to condition the filtrability of the tumors—namely, age of the hosts, age of the tumors, and source material used in inducing the tumors—did not appear to have any significant influence upon the titers of the filtered or unfiltered extracts of the tumors. These results are apparently at variance with those of Carr (6), who found the virus titer to be inversely proportional to the age of the tumors. An explanation of the discrepancy can be the fact that, contrary to us, Carr used highly inbred strains of chickens.

Reversion of the Masked Virus to a Free State

The possibility that the virus was present in the nonfiltrable tumors in a changed or masked form was considered. Passage of the tumors by cell suspensions into other hosts could be a means of revealing its presence. This was done with eight of our 33 nonfiltrable tumors. Six of these tumors had grown in adult hosts and two in young hosts. Of the adult-grown tumors, two were passed into other adults and four into young hosts. The two tumors grown in young hosts were passed into other young hosts. The results were clear-cut: all the resulting tumors yielded active filtrates when tested in the usual way. Evidently, no masking effect took place in the new hosts, either adult or young, and the virus reverted to a free, active form in all cases.

This reversion of the virus was further verified in a number of chicks inoculated with another nine of the 33 nonfiltrable sarcomas. The resulting tumors in these chicks were not tested for filtrability, but the occurrence of secondary lesions of the old chickens and gave inactive filtrates, could not be transmitted by cells. The transmissible tumors gave different proportions of takes in the test chicks. The results of these tests, pooled for different classes of tumors, are presented in Table 2, where the original tumors are classified according to the age of the host, age of the tumor, and filtrability.

In order to ascertain the degree and significance of the influences exerted by these three factors and by the source material of the original tumors upon their transmissibility by cells, a similar method of statistical analysis was used as in the study of transmissibility by filtrates. The analysis showed the following: (a) tumors induced by filtrates did not differ significantly in transmissibility from tumors induced by cells; (b) older tumors were significantly less transmissible than younger ones; (c) filtrable tumors grown in adult chickens did not differ significantly in transmissibility from filtrable tumors grown in young chickens; (d) nonfiltrable tumors grown in adult chickens were significantly less transmissible than nonfiltrable tumors grown in young chickens; (e) nonfiltrable

### Table 2

<table>
<thead>
<tr>
<th>Age Group of Original Tumors</th>
<th>Filtrable Tumors</th>
<th>Nonfiltrable Tumors</th>
<th>Filtrable and Nonfiltrable Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Hosts (Days)</td>
<td>Age of Tumor (Days)</td>
<td>Proportion in Test Chicks</td>
<td>Age of Tumor (Days)</td>
</tr>
<tr>
<td>Young</td>
<td>18.9</td>
<td>21.0</td>
<td>18.9</td>
</tr>
<tr>
<td>&gt;40</td>
<td>50.0</td>
<td>55.3</td>
<td>50.0</td>
</tr>
<tr>
<td>All ages</td>
<td>29.6</td>
<td>38.5</td>
<td>29.6</td>
</tr>
<tr>
<td>≤90</td>
<td>14.3</td>
<td>20.5</td>
<td>14.3</td>
</tr>
<tr>
<td>91-40</td>
<td>24.3</td>
<td>33.8</td>
<td>24.3</td>
</tr>
<tr>
<td>41-60</td>
<td>33.5</td>
<td>46.1</td>
<td>33.5</td>
</tr>
<tr>
<td>&gt;60</td>
<td>38.9</td>
<td>76.6</td>
<td>38.9</td>
</tr>
<tr>
<td>All ages</td>
<td>54.0</td>
<td>40.6</td>
<td>54.0</td>
</tr>
<tr>
<td>31.3</td>
<td>148/164</td>
<td>40.3</td>
<td>31.3</td>
</tr>
<tr>
<td>31/32</td>
<td>81.4</td>
<td>251/283</td>
<td>31/32</td>
</tr>
</tbody>
</table>
tumors grown in young chickens did not differ significantly from filtrable tumors grown in young chickens; and (f) nonfiltrable tumors grown in adult chickens were significantly less transmissible than filtrable tumors grown in adult chickens.

In brief, there was a significant decrease in the transmissibility of tumors by cell suspensions—first, with an increase in the age of the tumors and, second, for tumors of the same age in adult chickens, with the absence of free virus as manifested by nonfiltrability.

**Incidence of Metastases in the Original Hosts**

Among 80 chickens of whose tumors the filtrability was studied, 31 (38.8 per cent) had visceral metastases: 25 in the lungs, seven in the liver, three in the heart, and one in the ovary.

In Table 3 the incidence of metastases is shown in relation to the age of the hosts, age of the tumors, and source material which induced the tumors. According to the raw figures, the tumors induced by cell suspensions as well as those induced by filtrates gave more metastases when grown in young chickens than when grown in adult chickens. Also, in young as well as in adult chickens, the tumors induced by cell suspensions metastasized more often than those induced by filtrates. Moreover, a lower incidence of metastases was observed, in general, when the primary tumors had grown for a longer period before the hosts were killed—older tumors, as contrasted with young tumors.

The inverse relation between the incidence of metastases in the original hosts and the age of the primary tumors in the same hosts was probably only apparent, since one cannot assume that the metastases of an early age disappeared as the tumors grew older. This point will be considered in a following paper. In order to evaluate the significance of the effects of age of the hosts and source material of the tumors upon their metastasizing power, the relation between tumor age and incidence of metastases had to be taken into account in the statistical analysis.

Dose-response curves were calculated with data from Table 3 in the same way as in the study of transmissibility by filtrates, described above. The combined slope of the calculated regression lines was not statistically significant, showing that the age of the tumors was not significantly related to the incidence of metastases. Therefore, the effects of age of the hosts and of source material were tested as a $2 \times 4$ contingency table with $x^2$ based upon the pooled figures for all tumor ages. This $x^2$ ($= 5.153$) was not significant.

| Table 3
<table>
<thead>
<tr>
<th>Original Tumors Induced by Cell Suspensions</th>
<th>Original Tumors Induced by Filtrates</th>
<th>All Source Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Group</strong></td>
<td><strong>Original Tumors</strong></td>
<td><strong>Age Group</strong></td>
</tr>
<tr>
<td>of the Original Hosts</td>
<td>in days</td>
<td>Geometric mean</td>
</tr>
<tr>
<td>Young</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20</td>
<td>17.2</td>
<td>4/7</td>
</tr>
<tr>
<td>21-40</td>
<td>22.0</td>
<td>2/2</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>50.7</td>
<td>4/7</td>
</tr>
<tr>
<td>All ages</td>
<td>25.4</td>
<td>10/16</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20</td>
<td>23.2</td>
<td>1/3</td>
</tr>
<tr>
<td>31-40</td>
<td>51.5</td>
<td>5/5</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>44.9</td>
<td>8/5</td>
</tr>
<tr>
<td>All ages</td>
<td>75.7</td>
<td>0/5</td>
</tr>
<tr>
<td>All host and tumor ages</td>
<td>35.3</td>
<td>10/32</td>
</tr>
</tbody>
</table>

In brief, neither the age of the host nor the kind of material—filtrate or cell suspension—that induced the original tumors showed statistically significant influences on the incidence of metastases.

On the other hand, the incidence of metastases in the original hosts appeared to be significantly associated with the transmissibility of the respective primary tumors either by filtrates or by cells, as shown in Tables 4 and 5. In other words, the absence of free virus, a lower degree of transmissibility by cells, and the absence of metastases occurred as associated phenomena.

**Some Additional Observations on the Tumors Studied**

**Latent period.**—Our data on the latent period of the original tumors are only approximate, since the inoculated animals were usually examined at intervals of 7–10 days. The time that elapsed between the inoculation and the middle of the interval between the last negative and the first positive examinations was taken as the latent period of a tumor. If a growth was already present when the
animal was first checked, the latent period was assumed to be one-half of the interval between the day following the inoculation and the first examination. In relation to the ages at which the original tumors were tested and for each group of host age, the averages in days of the observed latent periods were as follows: Tumors from young chickens—less than 20 days, 8.1; from 21 to 40 days, 14.0; more than 40 days, 28.8. Tumors from adult chickens—less than 20 days, 8.1; from 21 to 40 days, 14.0; more than 40 days, 17.5.

Thus, increasing ages of the original tumors corresponded to increasing latent periods, especially in young chickens. On the other hand, the ages of the original tumors were in general inversely related to their speeds of growth, since usually tumors that grew fast were tested earlier in their development, whereas those growing slowly were tested at later ages. Therefore, one may say that, in general, the latent periods of the original tumors were inversely related to the speeds of growth of these tumors before they became noticeable.

Since it was known from previous studies that the dose of the inoculated virus is inversely related to the latent period (5) and directly related to the rate of growth (8), these results add further information concerning the inverse relation existing between content of free virus and age of the tumors.

On the other hand, no significant correlation was found between latent period and age of the host or source material inoculated.

#### TABLE 4

<table>
<thead>
<tr>
<th>TUMORS BY CELL SUSPENSIONS</th>
<th>Metastasizing original tumors</th>
<th>Nonmetastasizing original tumors</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing tumors</td>
<td>95</td>
<td>156</td>
<td>251</td>
</tr>
<tr>
<td>Not developing tumors</td>
<td>9</td>
<td>44</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>104</td>
<td>199</td>
<td>303</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 9.560 \]

\[ P = 0.002 \]

#### TABLE 5

<table>
<thead>
<tr>
<th>Filtrates</th>
<th>Metastasizing original tumors</th>
<th>Nonmetastasizing original tumors</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>27</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>31</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 14.200 \]

\[ P < 0.001 \]
Two points, closely related to each other, must first be considered concerning the masking of the virus.† The first is whether the change in the virus is of a quantitative or a qualitative order; the second is whether the virus is inactivated in the growing tumor or in the process of preparing the extracts.

With the data at hand no definite conclusions can be reached, although the following facts argue that, at least partly, masking is a qualitative phenomenon taking place in the growing tumor:

First, as shown in this study, free virus is more frequently found in extracts of the tumors induced by cells than in extracts of tumors induced by filtrates. Such a fact certainly cannot be explained by events taking place during processing of the tumor, whereas, as we shall discuss later, it could be explained by phenomena operating in the living animal.

The second fact is that in the Rous sarcoma, as in other virus infections, the minimal infective dose is an extremely small amount of virus, probably just one virus particle (9, 12), and, therefore, one such particle present in the filtrate injected would be enough to induce a growth.

The third fact is from a forthcoming study, the results of which must necessarily be here advanced: viruses from old sarcomas that still remained filtrable induced tumors with a significantly lower incidence of metastases than the tumors induced by viruses from young sarcomas. Thus, a qualitative change had occurred in the virus before it became masked in the aging tumor.

The above could lead to the assumption that masking of the virus is the result of a further effect from the aging host acting on the tumor. Then, the effect of the tumor age, as described by others (6, 7) and confirmed in the present investigation, would be a natural consequence of the action of the age factor acting in a cumulative fashion as the age of the tumor increases.

As to the effect of the source material, the virus in filtrates would be exposed to the age factor from the moment of inoculation, whereas the virus associated with cells would be protected at the critical moment of inoculation. This protection would go on during the first stages of formation of the tumor, if we consider that the tumor may get its start from multiplication of the inoculated cells. If the interpretation of these differences is correct, it would carry two implications of interest. The first is that the many generations of virus units derived from those originally present in the filtrates injected kept either a high degree of susceptibility to the age factor or an imprint of the initial masking effect. This would hold true even if one assumes that the virus has been acted upon by immune bodies or other agents during the preparation of the filtrates. The second implication is that the protection afforded the virus by the cell against the masking effect of the age factor is only relative, since tumors induced by cell suspensions also become nonfiltrable in the course of time.

Whatever the nature of the phenomenon, it would seem logical to assume that masking of the virus on the one hand, and impaired activity of the malignant cell such as low transplantability and low metastasizing power on the other hand, are related rather than coincidental phenomena. This would lead to the conclusion that, as discussed elsewhere (10, 11), properties of the malignant cell are conditioned by properties of the causative virus, and that the effect of the age factor on the cell is at least to some extent exerted through an effect on the virus. Whether the age factor can also exert a depressing effect on the malignant cell independently from a virus effect is, of course, a possibility, but suggestive facts in chicken tumors are thus far lacking.

The change induced in the virus by the age factor is only transitory and reversible in nature, for, by the simple expedient of transplanting tumor cells from a nonfiltrable tumor into other hosts, especially young hosts, free virus is easily recovered; conversely, free virus from a young host easily becomes masked in an old host.

These facts may be accepted as a reasonable explanation of the irregularity in the detection of virus in chicken tumors, especially when these are propagated through adult hosts, as is generally the case.

**SUMMARY**

The filtrability of the Rous sarcoma is inversely related to the age of the hosts and age of the tumors. Also, the tumors induced by cell suspensions have a higher filtrability than those induced by filtrates.

The transmissibility of the tumors by cells is inversely related to the age of tumors and, under certain conditions, directly related to their filtrability.

The occurrence of metastases is directly related to the filtrability of the tumors and to their transmissibility by cells.

Virus can be recovered from the nonfiltrable tumors by passage of the sarcoma cells into other hosts.

† There are several points in common between the subject here discussed and that concerned with the masking of the papilloma virus in rabbits. Pertinent papers (15–17, 20, 21) and still others can be consulted in this regard.
The findings are discussed in relation to the effect of the age factor on the tumor and its causative virus.

ADDENDUM

While this paper was in press a study has been published (E. A. Eckert, D. G. Sharp, D. Beard, and J. W. Beard, J. Nat. Cancer Inst., 12:533-42, 1952) showing that the infectiousness of the virus of erythromyeloblastic leukosis is inversely related to the length of the interval between the inoculation and the bleeding of the donor bird. The analogy between those results and these here presented is pointed out by the authors: This "brings erythromyeloblastic leukosis into line with the chicken sarcoma and rabbit papillomatosis with respect to the occurrence of masked virus."

REFERENCES

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