PATHOLOGY

Carcinogenic Activity of Some Fluorinated Polycyclics

CARCINOGENIC hydrocarbons, substituted by fluorine especially in the *K*-region, have been synthesized recently in a number of laboratories. As fluorine substitution alters the geometrical form of the parent molecule only very little, while it can be expected to have a marked effect on the electron density¹, its effect on the carcinogenicity of the parent compound may well help in further elaboration of the theories existing in this field.

Chalvet and Mason² have predicted with the help of a simple model that in 10-methyl-1,2-benzanthracene:

fluorine substitution in 1', 2', 3', 4, 6, 8 and 9 will lead to carcinogenic compounds, in 3 and possibly in 5 and 8 to non-carcinogenic substances. The results of Miller and Miller^{3,4} are in accord with this prediction, so far as the 3', 4-, 6- and 7-fluoro-10-methyl-1,2-benzanthracenes are concerned.

It may be of interest that, like 3-fluoro-10-methyl-1,2-benzanthracene, 3-fluoro-9,10-dimethyl-1,2-benzanthracene⁵ is not carcinogenic (or very little so), while 3-fluoro-9-methyl-1,2-benzanthracene⁶ has proved to be a highly carcinogenic compound. 3-Fluoro-6-methyl-benzanthracene⁷ shows no carcinogenicity. On the other hand, 4-fluoro-1,2,5,6-dibenzanthracene⁸ is strongly carcinogenic.

We have also investigated⁹ two fluorinated derivatives of 1,2-benzacridine—from which some highly carcinogenic substances are derived⁶.

namely, 3-fluoro-6,10- and 3-fluoro-7,10-dimethyl-1,2-benzacridine: the former is slightly (1/20), the latter more markedly carcinogenic (3/20). In the Walker inhibition test, the two benzacridines as well as 3-fluoro-9-methyl- and 3-fluoro-9,10-dimethyl-1,2-benzanthracene have proved active.

In view of the approximately equal carcinogenicity of 9-methyl-, 10-methyl- and 9,10-dimethyl-1,2-benzanthracene⁷, the exceptionally high activity of 3-fluoro-9-methyl-1,2-benzanthracene is unexpected.

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² Chalvet, O., and Mason, R., *Nature*, **192**, 1030 (1961).

³ Miller, E. C., and Miller, J. A., *Cancer Res.*, **20**, 133 (1960).

⁴ Miller, E. C., and Miller, J. A., *Proc. Amer. Assoc. Cancer Res.*, **3**, 134 (1960).

⁵ Bergmann, E. D., and Blum, J., *J. Org. Chem.*, **27**, 527 (1962).

⁶ Lacassagne, A., Bui-Hoi, N. P., Dandiel, R., and Zajdela, F., in *Advances in Cancer Research*, **4**, 315 (Academic Press, 1956).

⁷ See Badger, J. M., in *Advances in Cancer Research*, **2**, 104 (Academic Press, 1954).

Random Distribution of Affected Birth Ranks in Anencephalic and Spina Bifida Sibships with Two Affected Cases

In a recent investigation of anencephalus and spina bifida in New York State¹ it was demonstrated that these malformations have an increased incidence in siblings of affected cases. Since sibships with more than one affected member afford an opportunity to examine possible contagious or time-limited factors which might be involved in the causation of these malformations, the following investigation was carried out.

An alphabetic listing by last name was prepared of all cases of anencephalus and spina bifida (spina bifida, meningocele, meningomyelocele, myelocele, rachischisis) reported to the New York State Department of Health on birth records during the years 1945-60 inclusive. These cases were available in punch card form prepared in another investigation².

All individuals with the same last name were traced to their respective birth certificates. Children having the same last name, father's given name, and mother's maiden name, were considered siblings. In each case where two or more members of a sibship were found to have these malformations, total sibship size was determined by locating the last birth recorded to their mother in the Health Department birth indexes, and noting the birth rank of that birth.

One hundred and twelve sibships with two affected individuals, and four sibships with three affected individuals were found. In the 112 doubly affected sibships there were 24 sibships in which both cases were anencephalic, 42 sibships in which both cases were spina bifida, and 46 sibships in which one case was anencephalic and the other was spina bifida.

Table 1. ANENCEPHALIC AND SPINA BIFIDA SIBSHIPS WITH TWO AFFECTED INDIVIDUALS, UPSTATE NEW YORK, 1945-60; SIBSHIP SIZE

Sibship size	2	3	4	5	6	7	8	9	11	12	16	Total
No. of sibships	8	21	27	23	9	8	3	5	1	1	1	112

Table 2. ANENCEPHALIC AND SPINA BIFIDA SIBSHIPS WITH TWO AFFECTED INDIVIDUALS; INTERVAL IN YEARS BETWEEN BIRTH DATES OF AFFECTED SIBS, UPSTATE NEW YORK, 1945-60

Interval in years between births	0	1	2	3	4	5	6	7	8	9	10	11	Total
No. of sibships	3	21	33	14	10	6	13	4	3	2	2	1	112

Table 3. ANENCEPHALIC AND SPINA BIFIDA SIBSHIPS WITH TWO AFFECTED INDIVIDUALS. BIRTH RANK OF LATER BORN MIMUS BIRTH RANK EARLIER BORN, UPSTATE NEW YORK, 1945-60

Birth rank difference	1	2	3	4	5	9	Total
No. of sibships	62	27	14	6	2	1	112

Table 1 presents the 112 doubly affected sibships by sibship size. Table 2 presents the same sibships by interval between birth years of affected sibs. From Table 2 it may be seen that about one-half the time, the two affected sibs were born within two years of each other. Table 3 presents the 112 doubly affected sibships by difference of birth rank of the affected individuals. In more than half the sibships the affected cases occurred in consecutive birth ranks. A more detailed birth rank analysis is presented in Table 4. It can be seen that birth ranks are affected at random. That is, the observed distribution of affected birth ranks agrees closely with that expected by the operation of chance.

Assuming that the cases of anencephalus and spina bifida occurring in these sibships are similar to cases which occur singly, it would seem that the findings of this investigation minimize the role of causative factors which are contagious or limited in time. These findings would