this does not occur until 60 to 90 seconds after the intravenous injection. Such delayed muscular contraction is probably the result of a secondary, rather than direct effect of epinephrine.[2]

In the course of these experiments, it was noted that intravenous sodium pentobarbital anesthesia produced a delayed contraction of the denervated facial muscle in 11 of 12 tested monkeys. The contraction appeared after a latency varying from 16 to 60 seconds following the administration of 25 mg of sodium pentobarbital per kilo of body weight. The contraction could be elicited only by the intravenous route with a speed of not less than 10 mg per second. So long as the injection was rapid, the effect could be obtained even with subanesthetic doses.

The contraction induced with sodium pentobarbital lasted from 40 to 75 seconds. It could be so elicited so long as the muscle remained denervated. It was slightly enhanced by eserine and never blocked by atropine.

Similar results, and under the same conditions, were obtained with other barbiturates, such as sodium thiopentobarbital, sodium amytal, and sodium evipal. Intravenous injection of other anesthetics, such as paraldehyde, urethane, or ether inhalation did not produce contraction in the denervated face.

The mechanism of this contraction is difficult to explain. Barbiturates have no significant direct stimulation effect on striated muscle *in vitro*.[3] This, and the fact the contraction is delayed, suggest that the effect is indirect and secondary. It is possible that the rapid intravenous administration of barbiturate causes a physiologic disturbance in the body leading to the formation or release of substance causing the denervated muscle to contract. The nature and site of formation of this hypothetical substance are obscure. Because of its contractile effect on denervated muscle, the substance may be related to the cholinergic group.

[2] Bender, M. B., *Am. J. Physiol.*, 1939, **126**, 430.

[3] Goodman, L., and Gilman, A., *The Pharmacological Basis of Therapeutics*, Macmillan Co., N.Y., 1941.

14496 P

Genetic and Certain Non-genetic Factors with Reference to Leukemia in the F Strain of Mice.*

ARTHUR KIRSCHBAUM.

From the Department of Anatomy, University of Minnesota Medical School, Minneapolis, Minn.

MacDowell and Richter[1] found that the incidence of leukemia in hybrids could be roughly correlated with the total heredity from the high leukemia C58 strain when C58 mice were crossed with low leukemia StoLi animals. A "maternal influence" was suggested, for if the female parent was of the C58 strain the incidence of leukemia was greater than in the reciprocal cross. Cole and Furth,[2] working with the Ak and Rf stocks, concluded that susceptibility to leukemia is probably inherited as a multiple factor character, and is influenced by undetermined environmental factors. In various crosses the common logarithm of the percent leukemia was a simple function of the percent heredity from the high leukemia stock. Female mice had a higher incidence of leukemia than males. It was

* This investigation was aided by grants from The Jane Coffin Childs Memorial Fund for Medical Research and the Cancer Fund of the Graduate School of the University of Minnesota.

[1] MacDowell, E. C., and Richter, M. N., *Arch. Path.*, 1935, **20**, 709.

[2] Cole, R. K., and Furth, J., *Cancer Research*, 1941, **1**, 957.

TABLE I.

Table Summarizing the Data on Matings Between the High Leukemia F Strain and Strains A, CBA, and C57 (Low Leukemia Strains). Results were essentially the same when strain F mice were crossed with any one of the 3 low leukemia strains. The figure listed for each 100-day period gives the number of mice per 100 animals developing leukemia in that portion of the life span.

Age, days	High leukemia (F strain)	Backcross to high leukemia strain*	F_1 hybrids†	Backcross to low leukemia strain‡	F_2 hybrids
0- 100					
100- 200	3	2			
200- 300	7	9	0.5	1	1
300- 400	14	10	0.5	1	5
400- 500	13	10	6	1	7
500- 600	13	10	7	3	6
600- 700	3	9	11	11	6
700- 800		6	9	11	3
800- 900		0.5	8	3§	3
900-1000			7	1	6
1000-1100			2		
No. of mice	325	155	216	117	68

* Nine mice beyond 700 days of age still living.

† Fifteen animals living—over 900 days of age.

‡ Sixteen mice over 700 days of age still living.

§ Thirteen non-leukemic animals have died of polycystic kidney disease which is inherited as a recessive character from strain A.

concluded that the genetic basis for spontaneous leukemia may vary for different stocks of mice, since Mercier[3] had observed that susceptibility to spontaneous lymphosarcoma was inherited as a simple Mendelian recessive character, and the results of MacDowell and Richter were somewhat at variance with those of Cole and Furth. In later experiments with the Ak stock Furth, Boon, and Kaliss[4] found that when animals of this stock were crossed with the C3H rather than the Rf stock the incidence of leukemia in F_1 hybrids was higher, approximating that in the Ak stock, if the female parent was of the latter stock (50 as compared with 58%); the incidence of leukemia was 34% in F_1 hybrids of the reciprocal cross.

The present study was carried out using the F strain of mice as the high leukemia stock.[5] Of 325 control animals there were 173 cases of leukemia, or an incidence of 53%. Mice of the F strain were crossed with animals of strains A, CBA, and C57, in which the incidence of leukemia is less than one percent. Data on the breeding experiments are summarized in Table I.

In F_1 hybrids and backcrosses to the high leukemia stock the incidence of leukemia was approximately the same as in the pure F stock; in the backcross to the low leukemia stock the incidence of leukemia was decreased (Table I). The most significant finding would seem to be the delayed appearance of leukemia in the hybrid animals; this retardation was observed by MacDowell and Richter, and by Furth and his co-workers, although given little emphasis. Whether the delayed appearance of leukemia is to be correlated with the degree of inheritance from strain F or with the increased life expectancy in hybrids is difficult to say. The greater the number of strain F genes, the earlier leukemia appeared. However, life expectancy in F_1 hybrids was greater than in backcrosses to the F strain; leukemia also appeared later in life, but in approximately the same percent. For the heterogeneous F_2 population the appearance of leukemia was scattered through the various age groups. One of the observations which might indicate that the correlation is not entirely with life expectancy is that in backcrosses towards the low leukemia stock the life expectancy is not as great as in F_1 hybrids—still the first cases of leukemia appeared later than in F_1 hybrids. It might be that hybrids possess a greater degree of resistance towards

[3] Mercier, L., *C. R. Soc. de Biol.*, 1940, **133**, 29.

[4] Furth, J., Boon, M. C., and Kaliss, N., *Cancer Research*, 1944, **4**, 1.

[5] Kirschbaum, A., and Strong, L. C., *Am. J. Cancer*, 1939, **37**, 400.

the unknown causative "agent" of leukemia, and consequently the disease appears later in life and in a more chronic form. With an increased life expectancy metabolic differences might be expected to delay the onset of neoplastic change.

Concerning the incidence of leukemia in males as compared with females, in both hybrids and the pure F stock there was no significant difference in either the total incidence or the age distribution. Although administration of estrogens results in an increased incidence of leukemia in low leukemia stocks,[6] there is no evidence that sex hormones play a role in the spontaneous appearance of leukemia in strain F mice. Fifty-six strain F mice were gonadectomized at weaning age (34 males and 22 females). When no mouse was older than 525 days of age 17 of the castrate males and 10 of the 22 spayed females had developed leukemia. Gonadectomy did not alter the incidence of leukemia in either sex; the castrate atrophy of the male and female accessory sex organs indicated that the adrenal glands were not an extragonadal source of appreciable amounts of sex hormone.

There was no evidence for the existence of a leukemia "milk influence." Previous experiments on foster-nursing in this strain[7] indicated that a maternal influence, as for mammary cancer, is not operating.

[6] Gardner, W. U., Kirschbaum, A., and Strong, L. C., *Arch. Path.*, 1940, **39**, 1.

[7] Kirschbaum, A., and Strong, L. C., PROC. SOC. EXP. BIOL. AND MED., 1942, **51**, 404.

14497

Comparative Fibromatogenic Action of Ovarian and Urinary Estrogens.*

RAUL F. MELLO.†‡ (Introduced by Alexander Lipschütz.)

From the Department of Experimental Medicine, National Health Service of the Republic of Chile, Santiago.

So far all estrogens, natural or artificial, free or esterified, have been shown to induce abdominal fibroids when continuously administered to female guinea pigs for a certain time.[1,2] The urinary estrogen, estriol, also has been found to be fibromatogenic[3] though less so than estradiol or estrone, whereas with equilenin fibromatogenic action was insignificant[4] even when quantities twice or thrice those of estrone were absorbed. On the other hand, great increase of uterine weight and formation of endometrial polyps was also obtained with equilenin under these experimental conditions.[4] Equilenin has also been found to be less active than estrone in eliciting mammary adenocarcinoma in mice.[5]

One might tentatively suggest that presence of hysterotoxic and epitheliotoxic actions in the absence of fibromatogenic ones in the

* This investigation has been aided by grants from the Jane Coffin Childs Memorial Fund for Medical Research, and the Rockefeller Foundation, grants administered by Prof. A. Lipschütz.

† From the Section of Endocrine Glands, Santa Casa Hospital, Faculty of Medicine, University of Sao Paulo, Brazil.

‡ Thanks are due to Dr. Oliver Kamm of Messrs. Parke, Davis & Co. for estriol, equilenin, and the two dihydroequilenins; to Prof. A. Lipschütz for suggestions, and to Dr. S. Bruzzone for continuous help during my work.

[1] Iglesias, R., Tesis Universidad de Chile, 1938, *Public. Med. Exp.* (Chile), No. 1; Lipschütz, A., and Iglesias, R., *C. R. Soc. Biol* (Paris), 1938, **129**, 519; Lipschütz, A., and Vargas, L., *Lancet*, 1939, **1**, 1313.

[2] Lipschütz, A., *J. Am. Med. Assn.*, 1942, **120**, 171; *Cold Spring Harbor Sympos.*, 1942, **10**.

[3] Szabó, E., *Rev. Chil. Hig. y Med. Prev.*, 1940, **3**, 127.

[4] Thibaut, R., Tesis Universidad de Chile, 1941, *Public. Med. Exp.* (Chile), No. 7; Lipschütz, A., Thibaut, R., and Vargas, L., *Cancer Research*, 1942, **2**, 45.

[5] Lacassagne, A., *Ergebn. d. Vitamin-u. Hormonforsch.*, 1939, **2**, 259.