the C57 strains, even at 8.5 days gestation, seems to withstand the trauma of ionizing radiations better than either of the parental strains, as measured by subsequent embryonic development.

This study points up one more factor that may be overlooked, namely that heterosis shifts percentages toward a higher survival, but this includes a higher level of anomalies than among the very sensitive C57 strain. Thus, one sees here an example of heterozygosity aiding the survival of anomalies.

One might raise the question of the effect of reversing the hybrid cross, mating the CFl males with C57 females. Genetically there should be no difference, but it must be admitted that any cytoplasmic effects on the very early development might be involved. However, since the exposure to x-rays occurred long after implantation (which occurs at 4.5 days when the germ layers are forming) it can be assumed that any differences relating to the origin of the cytoplasm would have disappeared. Possibly heterotic influences are present at the moment of fertilization, only to be manifest later when tests are possible. Certainly they appear to be working at 8.5 days so that the more complicated investigations of earlier stages seem indicated.

Summary and conclusions. 1. Embryonic mice at 8.5 days gestation from pure C57 and CFl strains, and their hybrids, were x-irradiated to 200 r to determine whether prenatal heterosis was manifest. Criteria were the number of normal, resorbed, dead, or anomalous mice seen at 18.5 days in the hybrids as compared with the pure lines. 2. The hybrids at 8.5 days exhibited some degree of heterosis based upon the higher percentage of normal fetuses, and the lower percentage of resorptions when comparisons are made with the pure strain parental stocks. 3. For heterosis to be manifest, the hybrids had to overcome the severely deleterious effect of the presence of C57 genes as indicated by the 90% resorptions among this parental stock and only 30% in the hybrids, while the CFl showed 39%. Thus, there is evidence of more than mere dominance of the more resistant strain genes, hence heterosis at least by the time of organogenesis. 4. The heterosis for the embryo results in better survival, hence better survival also of the x-irradiation-produced congenital anomalies.

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Excretion of Urinary N-C^{14}-Methyl Morphine and Pulmonary $C^{14}O_2$ in the Monkey and Dog after Subcutaneous Injection of the Labelled Drug.* (26293)

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The application of radioisotopic tracer technics has provided much useful information on the biological disposition of the potent analgesic agents. March and Elliot(5), Elliot *et al.*(4), and Achor and Geiling(1) have studied the physiological disposition of C^{14}-labelled morphine in man, in rats and in mice, respectively. The present report of-

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TABLE I. Urinary Excretion of Free and Bound Morphine and Exhaled $C^{14}O_2$ in Monkey and Dog for the First 24 Hours after Subcutaneous Injection of 2.0 mg/kg of N-C^{14}-methyl Morphine.

	% of administered drug			
	Monkey		Dog	
	378	384	1	2
Urinary excretion*				
Free	6	14	13	15
Bound	55	71	48	52
Total	61	85	61	67
$C^{14}O_2$ excretion	1.5	.9	.2	.2

* Urine was cage collected as described in text. Dogs and monkeys were catheterized at the end of 24 hr period and urine so obtained was combined with the cage collected sample.

fers details of studies on physiological disposition of N-C^{14}-methyl morphine in monkeys and dogs.

Methods and materials. The N-C^{14}-methyl labelled morphine employed was synthesized according to the method of Andersen and Woods(2) and had a specific activity of about 2 μc/mg.

The studies on urinary excretion and $C^{14}O_2$ elimination were done according to the method of Woods *et al.*(9). Estimation of morphine in urine was performed according to the method of Mulé and Woods(7). *Animal studies*: Female animals were used throughout the study. Monkeys or dogs received 2.0 mg/kg of N-C^{14}-methyl morphine,‡ subcutaneously, and were placed immediately in the CO_2 collection apparatus. Both urine and $C^{14}O_2$ were collected for a 24-hour period. The animals were catheterized at the end of this interval and urine so obtained was added to the pan collected material.

Results. Urinary C^{14}-morphine and pulmonary $C^{14}O_2$ in dogs and monkeys. The results on urinary excretion of N-C^{14}-methyl morphine and elimination of $C^{14}O_2$ in the monkey and dog are summarized in Table I. Urinary excretion of free morphine 6-14%, bound morphine 55-71% and total morphine 61-85% in the monkey agrees well with the results of Mellett and Woods(6) on urinary excretion of morphine in non-tolerant monkeys given 15 mg/kg of morphine twice daily (free 10 ± 4.9, bound 67 ± 24.6 and total 77 ± 16.7). It would appear from these data that in the range of 2.0 to 30.0 mg/kg of morphine, total dose given does not significantly alter the pattern of drug metabolism in the monkey.

The results of $C^{14}O_2$ elimination in the monkey are of interest because the values appear to be very low when compared with $C^{14}O_2$ elimination after administration of N-C^{14}-methyl levorphanol, (0.9-1.5% for morphine *vs.* 17 to 24% for levorphanol) (Woods *et al.*,(9)).§

Urinary excretion of free morphine (13-15%), bound morphine (48-52%) and total morphine (61-67%) agree well with the figures of Cochin, *et al.*(3) free 14 ± 3%, bound 56 ± 9, and total 70 ± 1.1%. In the study of Cochin *et al.* non-tolerant dogs were employed and received a dose of 30 mg/kg, subcutaneously. These data would again indicate that the magnitude of the total dose in a range of 2.0 to 30 mg/kg does not significantly alter the drug metabolism pattern in this species.

$C^{14}O_2$ elimination by the dog after N-C^{14}-methyl morphine (0.2%) is similar to the low excretion of $C^{14}O_2$ found in this species after N-C^{14}-methyl levorphanol (1.0-1.5%).

Discussion. A number of factors may influence the pattern of metabolism of a given drug or series of drugs in various species. One of the factors generally considered important in modification of metabolism pattern is the dose. The results of these studies and those studies of Mellett and Woods(6) and Cochin *et al.*(3) indicate that in a dose range of 2.0 to 30 mg/kg of morphine there is no significant alteration in metabolic patterns of dogs or monkeys.

There is, of course, a wide variation in the manner in which various species metabolize morphine. However, within a given species closely related congeners of morphine may also be metabolized in quite different fashions. For example the monkey is capable of

‡ All doses are calculated as the free base although the drug was administered as a solution of the sulfate salt.

§ The same 2 animals were employed in both levorphanol and morphine studies after an interval of one year.

extensive N-demethylation of levorphanol (20%) as estimated by $C^{14}O_2$ elimination as compared with a limited ability to N-demethylate morphine (ca. 1%). The dog on the other hand appears to have little ability to N-demethylate either levorphanol or morphine. It is interesting that a similar pattern of O-demethylation of codeine obtains in the dog and monkey, *i.e.*, the monkey has a moderate capacity (8.0% of the dose) for O-demethylation while the dog has little or no capacity for this function (Woods *et al.*(8)).

It is apparent, therefore, that small changes in chemical configuration are capable of extensive modification of the metabolic pattern of the potent analgesics.

Summary. The results of urinary excretion and $C^{14}O_2$ elimination experiments in dogs and monkeys receiving 2.0 mg/kg of N-C^{14}-methyl morphine, subcutaneously, were as follows: dogs excreted 13-15% of total dose as free morphine and 48-52% as conjugated morphine and about 0.2% as exhaled $C^{14}O_2$. Monkeys excreted 6-14% as free morphine and 55-71% as conjugated morphine and about 1% as exhaled $C^{14}O_2$.

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Growth of Certain Arthropod-Borne Viruses in Hamster Kidney Tissue Culture. (26294)

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In recent years investigators have shown successful propagation of selected arthropod-borne viruses in various tissue culture systems(1-5) including hamster kidney tissue culture (HKTC). A single tissue culture system sensitive to many of the arthropod-borne viruses is particularly desirable. In our laboratory a long term study is being made to evaluate tissue cultures as host systems for isolation of viruses, study of virus cell relationships, and production of viral reagents. It has been our experience that hamster kidney (HK) cells are outstanding among the many cell lines under investigation in serving as a culture medium for an increasing number of viruses.

To evaluate HKTC as a suitable standard cell system for arthropod-borne viruses in respect to cytopathogenic effect (CPE), sensitivity, and viral growth, the present studies were made with 4 group A viruses: eastern equine encephalomyelitis (EEE), western equine encephalomyelitis (WEE), Sindbis, and Mayaro; and 5 group B viruses: Ilheus, St. Louis encephalitis (SLE), Japanese encephalitis (JE), Murray Valley encephalitis (MVE), and West Nile (WN).

Methods. Tissue cultures (TC) were prepared essentially according to Youngner's (6) technic. After 5-15 days, cultures containing full cell sheets and 1.5 ml of maintenance medium(7), were inoculated with 0.3