nicotinyl-hydrazides to patients and animals (7), in that the blocking of monoamine oxidase activity could conceivably lead to an accumulation of sympathomimetic amines with ensuing effects on the autonomic nervous system.

Summary. After the subcutaneous injection of 1-isonicotinyl-2-isopropyl hydrazine (IIH) into rats and guinea pigs, the monoamine oxidase activity of liver homogenates, liver mitochondria, and brain mitochondria is almost completely inhibited. The probable significance of such an inhibition is indicated.

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Dual Infection of Dogs with Distemper Virus and Virus of Infectious Canine Hepatitis.* (19911)

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Comparative studies(1) have shown that the illness produced by distemper virus resembles clinically the illness produced by the virus of infectious canine hepatitis. Both diseases were believed originally to be only one disease which was caused by the distemper virus, one of the earliest viruses isolated(2). Recent recognition of infectious hepatitis as a clinical entity(3) caused by a specific virus that produces characteristic intranuclear inclusion bodies, especially in hepatic cells, has now made possible the differentiation between this entity and that of distemper by histological studies. Shortly after the virus of infectious hepatitis was reported, mention was made of finding inclusion bodies of both distemper and infectious hepatitis in a dog that died from an illness attributed to distemper virus(4). Both distemper and infectious hepatitis have a high incidence rate(3,5). Following the report of inclusion bodies of both viruses in the same dog, further clarification seemed desirable. Studies were, therefore, undertaken in order to determine whether the two distinct viruses could infect dogs simultaneously, whether there would be discernible interference, and what the effects might be of such a concurrent infection. The results are reported herewith.

Experimental infection in dogs. Production. Puppies from 9 to 16 weeks of age were used and were obtained in litters of 3 or more. Prior to inoculation each litter was placed in an isolation unit and observed for at least a week for any sign of illness. During this period, temperatures and total leukocyte counts were taken daily. In instances where any puppy of a litter showed a temperature exceeding 39.5°C or a leukocyte count that deviated from the normal range, the entire litter was rejected. After the initial period of observation, puppies of each litter were divided into 3 groups and each group was placed in a separate isolation unit before inoculation. Each dog in 1 group was inoculated intravenously with 1 ml of a suspension in saline of spleen from a dog that had been given a strain of distemper virus originally obtained

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TABLE I. Comparison of Effects Produced in Dogs by Infectious Canine Hepatitis Virus (IH) and Distemper Virus (D) Singly and Mixed.

Virus	No. of dogs	Results of inoculation: Day of fever onset 1	2	3	4	5	Day died after inoc. 3	4	5	6	7	8	16+*	% died
IH	12		7	5				1	2	1	2	1		58
D	12		5	7									2	17
D and IH	28	26	2				12	4	4	1			1	79
D followed by IH	9	4	4	1			3	1	3	1				89
IH followed by D	5			4		1								0

* + means died 16 days or more after inoculation.

from the Fromm Laboratories. Each dog in the second group was inoculated intravenously with 1 ml of a suspension in saline of spleen from a dog that had been given Cornell Strain I infectious canine hepatitis virus, and each dog in the third group was inoculated with 2 ml of a mixture of equal parts of the same viral suspensions that were used for the other groups. Observations, temperatures and total leukocyte counts were recorded daily. These tests were repeated on 11 litters that represented 12 dogs in each group that received a single virus and 28 dogs the mixture. The results are presented in Table I.

Signs of illness. As can be seen in Table I, simultaneous infection with the viruses of infectious canine hepatitis and canine distemper produced a more severe illness in dogs than did either virus alone. In 26 of 28 dogs the incubation period was shortened from 2 days to 1 day. The percentage of deaths was higher, increasing from 17% for distemper and 58% for infectious hepatitis to 79% for both, and deaths resulted more quickly. In addition, the temperature and leukopenic reactions were more marked and the convalescent period of survivors was longer.

Presence of viruses in blood. From dogs that had been given both viruses at the same time, blood was obtained by venipuncture on the second day of fever, placed in sterile vials and stored under dry ice refrigeration. Then each of the 5 dogs that had survived inoculation with infectious hepatitis virus and subsequently shown to be immune to infectious hepatitis virus by a second inoculation was given intravenously 1 ml of the stored blood from a different dog that had been inoculated simultaneously. In like manner, 5 of the 9 dogs that had recovered from distemper and were shown to be immune by a second inoculation of distemper virus were each given blood from the same dogs that had furnished inoculation for those immune to infectious hepatitis. In addition, the other 4 dogs from the distemper-recovered group were given blood obtained from 4 other dogs that had been given the mixture of viruses. These results are also included in Table I. In all cases, dogs became ill and showed clinical signs referable to the respective viruses. That is, dogs that were immune to infectious hepatitis at the time of test developed distemper, whereas those immune to distemper developed infectious hepatitis. Blood from dogs given the mixture, therefore, contained both viruses during the febrile period.

Dogs immune to infectious hepatitis and then given the infective blood from dogs inoculated with the viral mixture developed an illness which resembled the disease in those given distemper virus alone. Dogs recovered from distemper and then given the infective blood, however, showed an illness which resembled that of the dual infection. Onset of fever was more rapid, the survival period was shortened, and the mortality rate was higher.

Presence of inclusion bodies. From 5 dogs that died, 3 on the third, 1 on the fourth and 1 on the fifth day after inoculation, thin slices of liver, lung and bladder were fixed in Zenker's, stained by Wilhite's method and examined for inclusion bodies of distemper and of infectious hepatitis. Typical intranuclear inclusion bodies of infectious hepatitis were found in hepatic cells of all dogs. One of the dogs that died 3 days after inoculation showed a few indistinct inclusions of distemper while the other 2 did not. The dog that died on the fourth day and the one on the fifth day

showed numerous well defined inclusion bodies of distemper.

Immunity. In tests for immunity, each of 5 animals that survived initial inoculation of the viral mixture was given intravenously, after 30 days, 1 ml of a suspension of single virus, followed in 21 days by a similar inoculation of the other virus. After inoculation, each animal was carefully observed, temperatures taken and leukocyte counts made. None of these animals showed signs of illness from inoculation with either infectious hepatitis virus or distemper virus. This indicated that immunity had developed against both of these diseases from the viral mixture.

Discussion. Following inoculation of infectious canine hepatitis virus and distemper virus simultaneously into dogs, both viruses were present in the blood during the acute phase of illness, inclusion bodies typical of distemper and infectious hepatitis virus were found in dogs that died, and immunity developed against both viruses. The conclusion was reached that dual infection had been produced in dogs.

A comparison of clinical signs shown by dogs that had received the mixture of viruses with those produced by each virus singly showed that signs of illness were more severe and a higher mortality rate was produced by the mixture. This finding may explain certain fatalities heretofore attributed to either distemper or infectious hepatitis, especially in instances where distemper virus is the precedent infection and thereby enhances the effects produced by infectious hepatitis.

The whole subject of dual infections or its converse, interference, presents many interesting aspects(6,7) particularly when related to the subject of immunization. Obviously, combinations of 2 or more viruses that produce dual or multiple infections simultaneously can permit combined vaccination procedures. In the case of infectious hepatitis and distemper, Poppensiek(8) has shown that dogs can be immunized consistently by a mixture of both viruses.

Summary. Following inoculation of distemper virus and infectious canine hepatitis virus singly and mixed, it was found that the mixture of viruses produced a more severe type of illness than either virus alone. In the same dog, both viruses were present in the blood during the acute phase of illness, inclusion bodies of both viruses were found and immunity against both viruses developed.

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Antitussive Action of *d*-Isomethadone and *d*-Methadone in Dogs. (19912)

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In the management of unproductive or useless cough (tussal insufficiency), potent analgesic drugs are generally employed. Among the active cough suppressants which have been used for this purpose are morphine, ethyl-morphine, codeine, dihydrocodeinone, and methadone. In addition to their antitussive action, these drugs have a general hypnotic effect, they are respiratory depressants, they are often nauseant, they produce constipation, tolerance develops to their use, and above all they possess addiction liabilities.

With the exception of the recent report of Toner and Macko(1), on experiments per-