The results obtained in these experiments suggest a probable explanation of the mechanism underlying the simultaneous consecutive passages of two animal viruses reported by previous investigators(11,12).

Summary. When mice were inoculated intraperitoneally with a mixture of *R. tsutsugamushi* and *R. typhi* it was found that both rickettsiae multiply simultaneously in the cytoplasm of the same cells lining the peritoneal cavity. The significance of this finding with regard to the simultaneous growth of other viruses in the same cell is described.

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Suppression of Gastric Acidity by Radio Krypton.* (19968)

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Radioactive Krypton, when contained in a balloon inflated in a dog's stomach, provides a safe, convenient procedure for suppressing gastric acidity. The induction of achlorhydria by roentgen therapy has been discarded because of inability to achieve adequate, intense selective radiation: the liver may suffer damage and necrosis, and in a few instances fatality has resulted(1,2). Simon(3) reported the use of P^{32} in suppressing acidity; while effective, the method was technically difficult because it involved the use of a double balloon with the phosphorus absorbed into cotton cemented to the outside of the inner balloon. McKendry(4) and Forse, McKendry and Webster(5) have used I^{131} for the same purpose, instilling it in solution so that it formed a thin film between the walls of a double walled balloon. In a series of well controlled experiments they were able to decrease the volume of secretion by gastric pouches without significant alteration of pH. *Exact local radiation* can be given only by an isotope with beta and no gamma emission. Most beta emitters such as P^{32} cannot be used inside a balloon because they must be dissolved in water—the water absorbs more than 90% of the radiation from the isotope in balloons of adequate size. However the absorption of beta radiation in a gas-filled balloon is negligible.

Two preliminary survey experiments were done with Argon 41 because of its 1.2 Mev beta emission. The dosage unit used is the "roentgen equivalent physical" or "rep" defined as that amount of beta radiation which, under equilibrium conditions, releases in one gram of air as much energy as one roentgen of gamma rays. A beta dosage of about

* Research carried out under the auspices of the Atomic Energy Commission.

12,000 rep to a Heidenhain pouch in one dog reduced the volume of histamine stimulated flow from 35 to 3 cc and changed the pH from 1 to 6 and the total acid from 140 units to 15 units. A Levine stomach tube with a condom tied to the end was placed within the stomach of a second dog. In five weekly treatments a dose in the neighborhood of 20,000 rep to the first 0.5 cm of mucosa was given in order to obtain an idea of what extreme doses would do. Gastric pH rose from 1 to 7. The dog ate most of his ordinary diet until the last two treatments when his daily consumption gradually dwindled until he refused to touch any food. The dog was sacrificed and the stomach examined by our pathologist, Dr. John T. Godwin. "Grossly the rugal folds are lost and the mucosa greyish and granular with minute hemorrhagic foci. Microscopically the mucosa is lost, being replaced by a fibrino-purulent layer. This extends into the submucosa in some areas. Beneath this are extensions of capillaries growing inward from the muscularis mucosa. There is proliferation of fibroblasts with large nuclei which are frequently encountered in post-radiated tissues. The submucosa is greatly thickened due to edema and a few inflammatory cells are scattered about." The use of radio Argon was discontinued because of its intense gamma emission which, while contributing little additional dose to the stomach, constituted a hazard to the operator.

Control experiments in 2 dogs in which balloons inflated with 350 cc of air were left in the stomach for 90 minutes weekly for 6 weeks showed no change in the initial pH of 1 or in the total acid which measured 125 to 140 units.

Krypton 87 has a 78-minute half life, emits beta radiation only, with a maximum energy of 3.2 million electron volts and penetrates tissue to a depth of about 1 cm. Krypton is forced into an aluminum container that is secured in the interior of the Brookhaven nuclear reactor. At the time of treatment several hundred cc of gas are collected in a copper coil; the coil sits in a Dewar vacuum flask and is immersed in liquid nitrogen so that the gas is frozen as it enters and builds up no pressure in the coil which holds 115 cc of gas at N.T.P. The coil may then be rapidly warmed, creating pressure within which is read on a gauge connected to the system.

Krypton 87, blown into a balloon at the end of a stomach tube, has been used in 2 dogs. Dog 1 required 4 treatments; dog 2, 7 treatments to suppress acidity. In each case the gastric juice was tested after a 24-hour fast and after the injection of 0.2 mg of histamine. From an initial pH of 1 and a total acid of 135 units, the pH has been elevated to 6 and the acid reduced to 12 units. The dogs have remained well, have eaten normally and lost no weight. The reaction of the gastric juice remains unaltered at pH 6 three months after treatment. Upon surgical exploration the gastric mucosa appeared grossly normal, and histologic examination showed no marked changes. "The mucosa of Krypton Dog 1 appears essentially normal with the exception of a mild mononuclear infiltration of the mucosa and scattered foci in which occasional glands have been lost. These glands have been replaced by a loose fibrous tissue. The parietal cells appear in normal numbers."

"Krypton Dog 2 showed some loss of normal architecture in several sections of the stomach wall. Some areas show a loss of glands which are replaced by a loose fibrous tissue containing scattered mononuclear inflammatory cells. In one area the mucosa has been destroyed and replaced by fibrous connective tissue which is covered by a single layer of epithelium. There are adjacent areas of epithelial hyperplasia with atypical glandular formations. The glands do not contain parietal cells and in addition the residual normally formed glands contain fewer parietal cells than those of a normal stomach."

Each treatment consists of 350 cc of Krypton instilled for 78 minutes (one half life). Specific activity is 30 microcuries of Krypton 87 per cc of gas. Krypton 85 is associated with Krypton 87—this is a weak gamma and beta emitter, has a 4.4 hour half life and makes no significant addition to the dose delivered.

Dosage delivered can be only very roughly approximated. Assuming the area of the dog's stomach to be 250 sq cm (Krypton Dog 2 was larger—area about 325 sq cm), and 1

cm penetration of the beta radiation, then 1 liter of Kr-87 will deliver about 300 rep to the gastric mucosa. However, half the total energy is absorbed in the first 0.15 cm of mucosa (half value thickness—0.032 $E_M^{1.33}$); this means about 2,000 rep were absorbed by this superficial initial portion.

Krypton is inert and balloon breakage would cause no serious damage. The length of each treatment and number of treatments required are reasonable. Blood counts in all animals remain normal. The chief difficulty is that at present the work must be confined to the neighborhood of a nuclear reactor.

Further more quantitative animal work and long time observation are required before advocating this treatment in hyperacidity associated with peptic ulcer. At present no contraindications have appeared.

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Effect of Substituted Hydrazines and Related Compounds on Myeloid Mouse Leukemia C-1498.*† (19969)

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Other investigators(1-5) have extensively studied basic nitrogen compounds comprising free amines, diaryl and dialkyl amines, guanidines and amidines in the chemotherapy of cancer. No comprehensive study has been made with compounds incorporating the hydrazine group. The ease with which hydrazines form hydrazones by conjugation with carbonyl compounds might possibly upset biological systems important for the promotion of tumor growth, particularly oxidation systems such as the citric acid cycle, wherein hydroxy-containing compounds are enzymatically oxidized to the corresponding carbonyl. It is possible that this hydrazone, resulting from the interaction of the hydrazine with the carbonyl group, might interfere with an essential oxidation-reduction process in the cell. Likewise, hydrazines react readily with glucose; in this way they might also interfere with intracellular carbohydrate metabolism. Sixty-six hydrazine and hydrazide derivatives are reported, including the following parent structures: phenyls, biphenyls, stilbenes, quinolines, naphthalenes, aliphatic as well as a few cyclic hydrazides. The compounds were chosen to give the greatest variations of chemical and physical-chemical properties.

Materials and methods. C-57 black mice were implanted subcutaneously with myeloid leukemia C-1498. Therapy was started the same day. Dosage was approximately one-half the maximum tolerated dose. Seven mice were used to evaluate each compound; in doubtful cases the experiment was repeated. The controls died in 12-14 days. The drugs were usually dissolved or suspended in 4% gum acacia solution; when necessary sorethitan monooleate was added to aid solution. Peanut oil was occasionally used. Drugs administered orally were given by stomach tube.

Results and discussion. The results are summarized in Table I, which is self-explanatory. None of the compounds showed any significant prolongation of life of the animals.

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