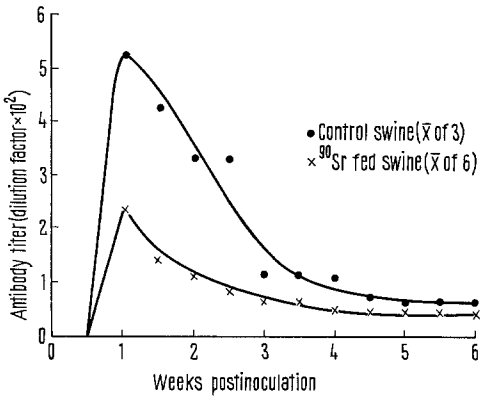
Immunosuppressive Effect of Chronic Strontium-90 Administration to Miniature Swine[1]

Pitman-Moore strain miniature swine have been fed daily doses of ^{90}Sr, through 3 generations extending over a period of 10 years, to determine the biologic effect of such a regimen and to ascertain the lowest dose level which would have no significant effect.

Strontium-90 is a beta-emitting radionuclide which is a bone seeker, competing with calcium for incorporation into the hydroxyapatite lattice of bone. Chronic exposure, such as by daily feeding of ^{90}Sr, results in a relatively uniform deposition of the radionuclide throughout the skeleton.

Leukemia has been the most frequently observed pathologic effect in these ^{90}Sr-exposed animals[2], although some osteosarcomas have also occurred[3]. Whether the leukemogen itself is considered to be an oncogenic virus or radiation, the immunologic surveillance system is often invoked in efforts to explain the leukemogenic process. This study was therefore conducted to determine the immunocompetence of miniature swine that had received chronic ^{90}Sr exposure.

Material and methods. The experimental protocol for our main ^{90}Sr exposure program has been previously described[4]. A separate group of Pitman-Moore miniature swine was selected for this study. The animals were 3 years of age; 6 were fed a daily dose of 625 μCi of ^{90}Sr and 3 served as controls. After the experimental animals had been fed ^{90}Sr for 10 months, they and the controls were given a single i.m. inoculation of 0.4 cm^3 of strain 19 *Brucella abortus* vaccine (Ft. Dodge Laboratories). Blood samples were taken biweekly for a period of 6 weeks following inoculation. Serum was separated and stored at − 60 °C until sampling was completed. The antibody titer was determined by the tube agglutination test using stained *B. abortus* antigen, and also using commercially titered antiserum (Sylvana Reagents) as a control.



Antibody response of Pitman-Moore miniature swine following *Brucella abortus* inoculation.

Results. Antibody response was not detected in either the inoculated or control swine until after the 4th day postinoculation. Maximum antibody titer was observed at 1 week postinoculation, at which time the level of specific antibody in the controls was more than twice that in the ^{90}Sr-exposed animals (Figure). This difference persisted throughout the observation period. By the 10th day postinoculation the titer was decreasing in both groups of animals, leveling off after about 28 days, at which time the titer of the controls still exceeded that of the ^{90}Sr-treated swine. The level of antibody response exhibited by the control swine is similar to that previously reported[5].

At the time of *B. abortus* inoculation there was no significant deviation from the normal hemogram in these ^{90}Sr-fed swine. Their clinical condition appeared normal, and at necropsy examination at the termination of this study, there was no significant histopathology.

Discussion. It was demonstrated in this experiment that prolonged ^{90}Sr exposure results in a significant immunodepression. Since the marrow is the hematopoietic tissue receiving the greatest radiation dose, we suspect that the defect in antibody response is a result of irradiating sensitive immunocompetent cells in this site. Both myeloid and lymphoid neoplasms have been produced in miniature swine receiving chronic ^{90}Sr exposure, possibly indicating that this radiation damage affects the pluripotent stem cell population in the marrow.

What role the chronic immunosuppression plays in the leukemogenic process has not been determined. Latent virus has been isolated from the leukemic swine of this study, but not from the control animals. Possibly the potentially oncogenic latent virus is allowed to express its effect when the antibody producing system is suppressed.

Zusammenfassung. Antikörperproduktion in Schweinen, die einer chronischen internen Strontium^{90}-Bestrahlung ausgesetzt waren.

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Absence of Haemolytic Effects of L-DOPA on Transfused G6PD-Deficient Erythrocytes

In vitro incubation of various concentrations of L-DOPA results in significant loss of GSH from G6PD-deficient and not from normal red cells[1]. Kosower and Kosower also suggest the possibility that DOPA and cathecholamines may contribute to the destruction of GSH under physiological conditions in G6PD-deficient individuals. These substances may be responsible, at least in part, for the shortened survival of G6PD-deficient red cells found in affected individuals not subjected to the action of oxidating drugs[2]. L-DOPA is used in neurology for the treatment of Parkinson's disease[3]. If the drug had some haemolytic effects it would be highly dangerous to

Studies with ^{51}Cr-tagged red cells belonging to G6PD-deficient subjects, transfused into normal recipients receiving L-DOPA, Primaquine, DDS

Donor	Sex	G6PD U/min/g/Hb	Recipient	Sex	Drug	Dose (mg)	Days of administration	^{51}Cr T/2 before drug administration (days)	^{51}Cr T/2 after drug administration (days)
C.A.	♂	0.00	R.A.	♀	DOPA	50	7	20	20
						50	7		
			C.A.	♀	DOPA	75	6	21	21
			O.A.	♂	Primaquine	45	1	18	6
B.M.	♂	0.00	S.G.	♀	DOPA	100	9	20	20
			B.S.	♀	DOPA	100	9	18	18
			S.R.	♀	DDS	50	9	19	8

administer it to G6PD-deficient patients with neurological diseases. This may occur in areas with high incidence of the enzymatic defect of the red cells[4,5].

The transfusion of ^{51}Cr-labelled G6PD-deficient red cells into normal subjects who then receive primaquine or other oxidating substances constitutes a valuable and well-established method in order to test the haemolytic effect of drugs[6,7] on G6PD-deficient red cells. This method has been utilized in an attempt to study the possible haemolytic effects of L-DOPA on G6PD-deficient red cells.

^{51}Cr-tagged, G6PD-deficient red cells belonging to 2 Sardinian male patients, one of whom had a past history of favism, were transfused into 4 normal recipients with compatible blood groups. After the baseline assessment of the ^{51}Cr half time, the 4 subjects received, in a fasting state, daily intravenous infusions of physiological saline containing 50, 75, or 100 mg of L-DOPA (Hoffmann-La Roche[8]) for periods ranging from 7–13 days. The infusion rate was of 1.6, 2.5, 3.3 mg/min respectively. No changes in the slope of blood radioactivity could be observed after the administration of L-DOPA (Table). The ^{51}Cr-tagged red cells belonging to the same two G6PD-deficient donors, transfused into normal recipients who received thereafter primaquine or diaminodiphenylsulfone (DDS), were rapidly destroyed.

In the study outlined above, the in vivo use of L-DOPA in quantities recommended for the treatment of Parkinson's disease does not impair the normal survival of G6PD-deficient red cells. It should be noted, however, that L-DOPA might possibly undergo a different metabolic breakdown in subjects affected by favism[9].

Riassunto. Eritrociti G6PD deficienti, marcati con Cr 51, sono stati trasfusi in soggetti normali cui venivano somministrate giornalmente dosi di L-DOPA per via venosa. La L-DOPA viene usata per la terapia del morbo di Parkinson, e causa in vitro una perdita di GSH dagli eritrociti G6PD deficienti. Non si sono osservate modificazioni nella curve della radioattività ematica come conseguenza della somministrazione della L-DOPA. Si conclude pertanto che tale farmaco non ha effetti emolizzanti sugli eritrociti con carenza enzimatica di G6PD.

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Platelet Protein Synthesis Studied in a Cell-Free System

The ability of circulating blood platelets to synthesize proteins has been well established[1,2]. Since platelets do not contain DNA[3] it is to be expected that the presence in them of a functioning messenger RNA may be limited in time resulting in a progressive decrease of protein synthesis in aging platelets. This indeed could be shown by comparing the rate of protein synthesis in populations of platelets of varying age[4].

Thrombosthenin, a contractile, actomyosin-like protein is abundant in blood platelets[5,6]. It is also the protein that is most actively synthesized by the circulating platelets[7]. There exist differences of chemical and biophysical nature between thrombosthenin of platelets and actomyosin of other cellular origin[6]. Although its exact function still remains to be elucidated, the occurrence of a contractile protein in platelets may be of special significance for their hemostatic function.

Polysomes, the visible evidence for active protein synthesis in cells, have never been unequivocally demonstrated in platelets by electronmicroscopy while single ribosomes have. In the present investigation, these necessary templates for protein synthesis were indeed