was very low at the beginning of the experiment. Once the peak was reached the daily urinary output of the vitamin C tended to be fairly constant which amounted to about 60% of the intake. The excretion dropped abruptly with the discontinuance of the added vitamin in the diet.

Following the increase or decrease of vitamin C supply in the diet there was a corresponding fluctuation in the vitamin C content of milk, but the change was very slow and steady, being entirely different from the type of response in the urinary excretion. Milk, being a product of secretion rather than excretion, seemed to behave like the body tissue in this respect. After it had reached a "saturation" level which was around 0.08 mg. per cc. the concentration of vitamin C in the milk remained quite high for about 10 days even after the extra supply of the vitamin was discontinued.

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Effects of Acetyl Salicylic Acid on the General Condition and Blood Cells of Rats.

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Published facts and opinions[1] regarding the low toxicity and safety of acetyl salicylic acid (aspirin) do not preclude the possibility that long continued daily use of this drug might be productive of bad results. This preliminary investigation, using white rats as subjects, was undertaken to test this possibility. The results were mainly negative.

Table I summarizes the results of administration of the drug to 33 young animals, 7 other animals constituting a control group. Weighed doses of acetyl salicylic acid were mixed with small portions of the standard mixed ration, and care was taken to assure that the entire dose was consumed each day. As compared with the control animals, the experimental animals were found to be normal in general physical condition, growth curves, appetite, activity, coat condition, and appearance of eyes, ears, tail and feces. Since doses of

[1] See esp. Editorial, *Lancet*, 1935, **229**, 619; Lowry, Otto, *Canadian Med. Assn. J.*, 1934, **31**, 638; Stiell, W. Fletcher, *Prac. London*, 1917, **99**, 293; Macht, David I., *Med. Record*, 1918, **94**, 767.

20 to 50 gm. of acetyl salicylic acid are mentioned in the records of fatal poisoning of adult human beings, we assume that 20/70 or 0.28 gm. per kg. of body weight marks the beginning of the lethal range for human beings. It is noteworthy that the 4 animals in Group VI received daily doses in excess of this for 7 weeks without observed effects.

TABLE I.
Summary of Experiments with Rats Dosed with Acetylsalicylic Acid.

Group	Period (beg. age, 5 wks.)	Daily dosage, gm./kg.	Human equivalent, 70 kg. body wt.		Results
	weeks		gm.	grains	
I.	25	.022	1.54	23.8	Normal
	29	.025	1.78	27.5	"
II.	15	.022 incr. grad. to .11	7.72	119	"
III.	24	.025 incr. grad. to .265	18.54	286	"
IV.	29	.025 incr. grad. to .127	8.9	138	"
V.	25	.034 incr. grad. to .408	28.5	440	"
	(At top level 1 week; in human lethal range 4 weeks)				
VI.	9 (beg. age, 13 wks.)	.17 incr. grad. to .623	43.6	672	"
	(In human lethal range for 7 weeks)				

Five animals unaccustomed to the drug were each given a single dose of acetyl salicylic acid equivalent to 39.6 gm. (611.4 grains) for 70 kg. body weight. They showed no toxic symptoms whatever. By mating rats which had been receiving heavy doses for 22 weeks perfectly normal litters were obtained. The treatment was continued throughout pregnancy.

Table II summarizes the results of blood cell counts of rats dosed for 14 weeks with .034 gm./kg. Since it has been shown by Warner[2] that the normal white rat shows a great deal of variation in white cell counts with variations in external temperature, light, food, water, sex activities and excitation by handling, and that a regular diurnal tide of considerable magnitude occurs, these conditions were regulated, and the diurnal tide was taken into account in interpreting the results. It is obvious that no substantial differences occur in the drugged animals as compared with the controls. Kerti[3] found that in human beings, a decrease of about 10% occurred in the red cell count after 2-4 days of aspirin administration.

When the drug was withdrawn from the ration of rats which had become accustomed to it, no visible symptoms of disturbance occurred, but the blood cell picture was affected for several days.

In a group of 11 male rats receiving gradually increasing daily doses for 18 weeks, the average dose being 0.1 gm./kg., we

2 Warner, Douglas, PROC. SOC. EXP. BIOL. AND MED., 1935, **33**, 230.

3 Kerti, *Wiener klin. Wochenschr.*, 1929, **42**, 1630.

TABLE II.

Summary of Blood Cell Counts	Aver. of: 9 exper. rats	8 controls
Total red count	8,150,800	7,916,210
Average deviation	445,080	380,416
Total white count	14,551	14,493
Average deviation	3,495	3,275
Distribution of white cells:	%	%
Lymphocytes	66.5	72.7
Monocytes	1.3	1.6
Polynuclear neutrophiles	24.7	20.9
Metacytes	3.8	3.2
Staff cells	0.9	0.7
Polynuclear eosinophiles	2.6	0.9
Polynuclear basophiles	0.4	0.2

find that the erythrocytes decrease somewhat on the second day after ceasing administration (perhaps due to blood dilution) return nearly to normal on the fifth day. The differential count shows increase of the polynuclear neutrophiles from a little over 20% to almost 40% on the second day, falling again gradually after 4 days; the metacytes and staff cells rise after 3 days, gradually fall on the fifth and sixth days; while the total leucocytes rise about 60% on the second day, return to normal about the sixth day.

Single doses failed to show substantial changes which could be attributed to the action of the drug. In such experimentation, it is necessary to establish the norm for each individual rat before giving the drug, and to anticipate the diurnal tide variations.

Summary. Daily dosage of white rats with acetylsalicylic acid for periods as long as 29 weeks, at high levels, produces no visible ill effects, and does not change the blood picture, except that a pronounced rise of white cell counts occurs on the second day after withdrawal of the drug from animals accustomed to it. It is obvious that the white rat is not suitable for testing the question of the possibility of ill effects in human beings from prolonged dosage with this drug.