However, the hypoglycemic action of the insulin injected 1 hour after the liver preparation was markedly increased. This statistically significant ($P < 0.001$ at 2, 3, and 4 hours after 0.5 unit/kg of body weight and $P < 0.05$ at 3 hours and $P < 0.01$ at 4 hours after 1.0 unit/kg of body weight) effect is illustrated in Fig. 1, where the blood glucose concentration is expressed as a percentage of the preinjection level.

Whereas the insulinase-inhibitor preparation was nontoxic for rats even at a dosage of 10 g/kg of body weight, it was toxic in rabbits at dosage levels as low as 1 g/kg of body weight. Occasional rabbits survived the subcutaneous injection of 1 or 2 g of the preparation per kilogram long enough to permit the determination of the hypoglycemic response to the intravenous injection of 0.1 unit/kg of body weight. Figure 2 illustrates the hypoglycemic response of a rabbit that lived about 18 hours after the subcutaneous injection of a solution containing 2 g of the preparation per kilogram of body weight.

In this experiment, the hypoglycemic response to the intravenous injection of insulin was tested in two rabbits. After a preliminary test in which both rabbits gave essentially the same response, one animal was given a subcutaneous injection of saline and the other an injection of the liver extract. One hour later, the hypoglycemic response to the intravenous injection of insulin was determined again. It is apparent that the injection of the insulinase-inhibitor preparation 1 hour before the insulin resulted in a marked increase in the biological effectiveness of the insulin. Similar results have been obtained with other rabbits that survived the injection of the liver preparation.

The data reported here reveal that a liver insulinase-inhibitor preparation that

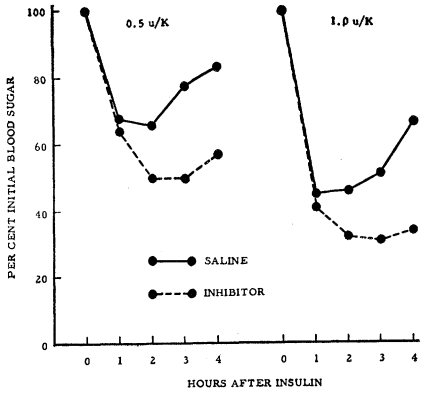

Fig. 1. Effect of insulinase-inhibitor on hypoglycemic action of insulin in rats. Response expressed as percentage of the blood sugar concentration immediately before the intraperitoneal injection of insulin.

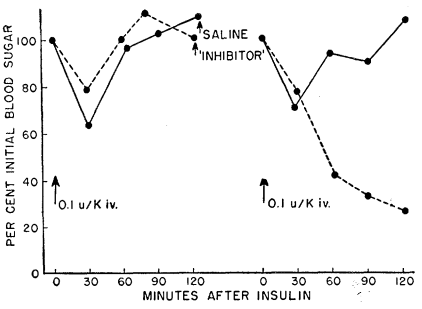

Fig. 2. Effect of insulinase-inhibitor on hypoglycemic action of insulin in rabbits. Two rabbits were given an intravenous injection of insulin at zero time. A second injection of insulin was given 1 hour after the subcutaneous injection of either saline or liver preparation. Response expressed as percentage of the blood sugar concentration immediately before each intravenous injection of insulin.

effectively inhibits the destruction of insulin *in vitro* and *in vivo* is effective also in increasing the biological activity of insulin in rats and rabbits.

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16 May 1955

Prenatal Ingestion of Fluorides and Their Transfer to the Fetus

McKay and Black have pointed out that factors influencing the integrity and structure of tooth enamel are effective only during the calcification period (*1*). It is logical then to assume that any beneficial effects from fluorides would be derived only while the teeth are in developmental stages when the matrix is being formed and the enamel is undergoing calcification or maturation.

On this premise, a long-range study was instituted in 1948 to determine the value of fluorides in preventing caries. The fluorides are given to the expectant mother during pregnancy and are also administered to the child until permanent tooth calcification has occurred (*2*). A final report of this work will not be made until the teeth of the offspring can be evaluated for their resistance to decay. This paper, a phase of the study, presents the results of an investigation to determine the relationship between maternal ingestion of fluorides, placental storage, transplacental passage, and fetal cord blood levels.

Past studies have mentioned the transfer of fluorides from mother to fetus (*3*) and have shown a positive correlation between fluoride supplementation and the fluoride content of the placenta (*4*). However, there is no report in the literature of an attempt to correlate the fluoride concentration of fetal blood and placental tissue in a study using fluoride tablets during the pregnancy.

Four groups of patients were used: (i) patients given one tablet of calcium fluoride (each 2 mg) (*5*) or sodium fluoride (each, 2.2 mg) per day. Treatment was initiated at various stages of pregnancy; (ii) controls, from the same locale, who had no known supplemental fluorides; (iii) individuals who drank artificially fluoridated water throughout their pregnancy; and (iv) controls from a nearby area that did not have a fluoridated water supply.

Sections of approximately 25 g of tissue were taken from the periphery of the placenta, and about 25 to 50 ml of blood was expressed from the umbilical cord after it had been severed. The fluorides were then separated by the Willard-Winter distillation (*6*) process and their concentration was determined by the William's titration method as modified by Smith and Gardner (*7*). Every possible precaution was taken to rule out any laboratory error. A constant and a percentage correction factor, as well as the standard deviation of 2.4 percent of the technique, were considered before the results given in Table 1 were reached.

The average fetal blood fluoride concentration in the tablet study group was 41 μg/100 ml; in the control, 17 μg/100 ml. The average placental fluoride concentration in the tablet study group was 111 μg/100 g; in the control, 101 μg/100 g.

In the fluoridated water supply study group, the average cord blood concentration was 38 μg/100 ml; in the control, 22 μg/100 ml. The average placental concentration was 85 μg/100 g in the study cases; 68 μg/100 g in the control.

In both study groups the average cord blood fluoride concentration was higher than it was in the respective controls. The concentration in the group that took fluorides by tablet was 250 percent higher than it was in the control; in the group that took fluoridated water, the concentration was 175 percent higher. Twenty percent of the tablet study group had a

Table 1. Fluoride concentration in cord blood and placenta

Group	No. of cases	Average fluoride concen.	
		Cord blood (μg/100 ml)	Placenta (μg/100 g)
Fluorides by tablet	20	41	111
Control	146	17	101
Fluorides from water	6	38	85
Control	9	22	67

fluoride concentration above 50 μg/100 ml, whereas only 3 percent of the control group had a concentration above this level.

This marked difference between the fluoride concentrations of the control and the study groups was not shown in the placentas. However, it is important to note that in neither study group was there any placental concentration of less than 25 μg/100 ml. But in the tablet control group, 7.5 percent contained less than this concentration, and in the fluoridated-water control, 11 percent contained less.

The large difference in the placental fluoride concentration in the two control groups may be explained by considering the amount of fluorides ingested in the normal diet in the two localities.

The role of the placenta in fluoride metabolism remains obscure. Two placentas, one from the tablet control group and one from the tablet study group, were selected at random and analyzed completely by sections for their fluoride content. The results are represented diagrammatically in Fig. 1. In both cases the fluorides were more concentrated in the periphery of the placentas. The reason for this distribution is not apparent at this time but two possible reasons can be offered. (i) Since the calcium content of the placenta is relatively high at the periphery (*8*), the distribution may be merely a chemical manifestation. (ii) The placenta may serve as both a storehouse and a regulator of the fluorides. In an attempt to prevent too much fluoride from entering the fetal blood stream at one time, the placenta pushes it away from the area of most active maternal-fetal exchange. In the periphery, the fluorides are stored and released as needed. Scant proof of this hypothesis may be found in the observation that the difference in the placental fluoride concentration between the study and control groups was not marked in either locality.

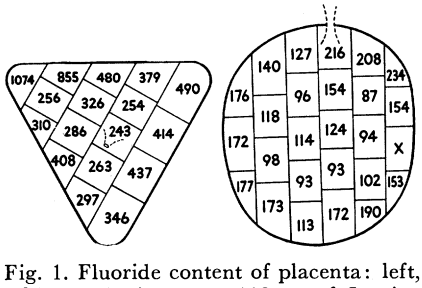

Fig. 1. Fluoride content of placenta: left, tablet study (average, 419 μg of fluorine per 100 g of tissue); right, tablet control (average, 141 μg of fluorine per 100 g).

The results of this study indicate that the fetal blood level can be increased by supplementation either in tablets or in water; however, the importance of this is difficult to assess at the present time because there is no known normal or optimum concentration. Besides an increased fluoride concentration in both the cord blood and the placental tissue of the study cases, no other correlation was demonstrated.

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26 May 1955

To Calculate Days between Two Dates

G. J. Cox [*Science* **121**, 779 (1955)] has presented a section of a counting house calendar for estimating intervals in days. A useful table for this purpose is found in *The World Almanac and Book of Facts*, which is published annually by the *New York World-Telegram and Sun*, a reference within easy reach of most laboratory workers. The table "Days between two dates" appears on page 412 of the 1955 edition. The arithmetic of the table is obvious.

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7 June 1955

The reference to the development of a calendar of "days elapsed" and "days remaining" by G. J. Cox is of more than passing interest. Such information is desired quickly in many fields of work. In our work we are constantly involved in a variety of problems that are simplified by the use of such a calendar.

However it is strange that so many scientists, engineers, and others are unaware of the simplest calendar of all—the Julian Day calendar—which enables Cox's example to be done by mental arithmetic, subtracting one number from another. For example, the Julian Day number is represented by seven figures and 1 Jan. 1951 is J.D. 2433647. However, usually only the last three or four figures are necessary.

30 Jan. 1955 = J.D. - - - 5138
28 Dec. 1951 = J.D. - - - 4009

Age in days 1129

There is no need to worry about leap year. We use a standard 100-year table showing the Julian Day number for the first day of each month from 1900 to 2000. One of the most widely distributed is the AAVSO Julian Day calendar, which has been produced for many years by the American Association of Variable Star Observers. The AAVSO J.D. calendar for 1955 was printed by the United Scientific Co., for the AAVSO and distributed by both organizations. The American Ephemeris also includes a summary J.D. calendar covering the period A.D. 0 to A.D. 2019 for use where longer periods of time are required. The J.D. calendar deserves a more widespread use, for it eliminates a lot of mental and physical effort, and answers all of Cox's problems.

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16 June 1955

Science carries us into zones of speculation, where there is no habitable city for the mind of man.—ROBERT LOUIS STEVENSON.