Persorption of Particles: Physiology and Pharmacology

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I. Introduction

A. Absorption—Persorption

In the molecular form, i.e., in solution, substances are transported through the epithelial enterocytes of the small intestine. Very small particles in the nanometer size range can also be transported through the enterocytes by way of pinocytosis. Earlier, however, it was considered

impossible for large solid particles in the micrometer size range to cross the barrier of the intestinal mucosa—despite the observation made long ago that large, solid, insoluble, nondeformable particles somehow succeed in passing from the digestive tract into the bloodstream. The earliest reports that orally ingested particles could be detected in the blood were made by Herbst (1844), Oesterlen (1846), Marfels and Moleschott (1854), Hirsch (1906), and Verzar (1911), but these findings were assumed to be either misapprehensions or the result of impurities in the materials used. This phenomenon, to which the name *persorption* has now been given, has been the subject of a thorough and systematic investigation by the present author (Volkheimer, 1964, 1968, 1972, 1974).

B. Initial Studies

In a long series of preliminary studies (Volkheimer, 1964), it was found that the oral application of native starch was followed after only a few minutes by the appearance in the blood and urine of starch granules of the same kind as those ingested. Special precautions were taken to exclude any possibility of contamination of the material examined by carrying out a large number of control tests. The specific microscopical structure of the starch granules made it impossible for any error or misapprehension to occur. The same phenomenon was observed when polyvinyl chloride (PVC) particles were used as the model substance.

C. General Methods

1. *Model Substances*

The experimental work to be described in this review is limited to the persorption of starch granules of various diameters, such as cornstarch (3–25 μm), potato starch (5–110 μm), and rice starch (3–10 μm) granules. Other particles, e.g., diatoms (5–150 μm), pollen (10–120 μm), PVC (5–100 μm), and other particulate matter have been used successfully (see Section II,E).

2. *Vehicles*

Homogeneous suspensions of 200 gm have been prepared in water, cold tea, or buttermilk for consumption by human volunteers. Dogs took doses of 50–250 gm of starch particles in water, but preferred cream, although this vehicle owing to its fat content increases the persorption during the first 90 minutes. In humans this increase is delayed (Volkheimer, 1972).

3. *Administration*

Small animals, e.g., chickens, were treated with 20 gm cornstarch by gastric intubation; rats, mice, or guinea pigs were used for special studies of phagocytosis and received starch granula by either oral or rectal administration. Human subjects and dogs consumed the particle suspensions by drinking.

It is important that no particle residues are in the system of the test animals or humans. The experiments were, therefore, carried out in animals after 24–36 hours fasting, in human volunteers after 3 days of starch-free diet.

Further details of the test procedures, particularly the counting of particles in the blood, are described in the following sections. It may be mentioned, however, that particles in other body fluids, such as urine, cerebrospinal fluid, bile, and chyle, are also demonstrated and counted in the centrifuged sediment, occasionally (bile, chyle) with dilution of viscous specimens in water.

II. Mechanism of Persorption

The mechanism by which particles pass through the epithelial cell layer was studied on the rat intestine.

A. Model Substances

Starch granules are a suitable model substance for studying the mechanism of persorption in the wall of the intestine since they are readily identifiable in body fluids and tissue sections.

B. Methods and Results

When rats have been fed with starch, tissue sections prepared from the wall of the digestive tract reveal the presence of occasional starch granules in between the epithelial cells. Others are seen in the subepithelial region and in the lumen of lymph and blood vessels. These findings demonstrate that paracellular passage through the epithelial cell layer is the persorption route for such large, solid, nondeformable particles. This is possible where the intestinal mucosa is covered by a single layer of epithelium. Mechanical factors are mainly responsible for the persorption process. Movements of the structures in the digestive tract as well as the vascular pulsations transmitted to the mucosa play an important part in the transepithelial passage of the particles.

C. Further Transport of Persorbed Particles

The further transport of persorbed particles takes place via both the chyle and the portal circulation.

1. *Transport by Chyle*

That starch granules are transported by the chyle is shown by the observation that they are found only in the lymphatics of those segments of the digestive tract containing starch. Lymphatics of segments free of starch contain no starch granules.

2. *Portal Transport*

Portal transport of starch granules is demonstrated by a quantitative comparison of the numbers of granules in blood samples taken simultaneously from mesenteric veins and from the aorta of dogs fed with starch. The mesenteric venous blood from segments of the digestive tract in which starch is present contains significantly more starch granules than arterial blood. Control observation: rather fewer starch granules are found in the mesenteric venous blood from starch-free intestinal segments than in the arterial blood.

D. Persorbability of Particles

The persorbability of particles is limited by their size and hardness. For experimental observations, hard particles with a diameter between 7 and 70 μm give the best results.

For PVC particles and rounded quartz particles, the upper size limit for persorbability has been found to be 150 μm. When fed to dogs, such large particles were, however, found only very rarely in the chyle. Particles with a diameter of 70 μm are regularly found in this fluid.

Using smaller particles, the lower size limit for persorbability has also been studied. Paracellular transport of particles about 5 μm in diameter was observed. This is also possible, however, for even smaller particles, as is evidenced particularly by the passage of yeast cells and bacteria through the mucosa.

E. Persorbable Particles

1. Observations of persorption *in man* have been made by the author on himself using various model substances. After enteral application (oral, rectal), diatoms, pollen, spores, cellulose particles, plant cells, and

starch granules were regularly demonstrable in the body fluids (blood, urine) (Volkheimer, 1964).

2. *Experimental animals* (mainly dogs) were fed the same substances as in the foregoing observation and also colored particles obtained by grinding crab and lobster shells, fish meal and bone meal, PVC and other plastic particles, metallic iron powder, parasite eggs, asbestos fibers, fragments of animal hairs, powdered industrial diamonds, silicates, crystals, etc. All these particles could be demonstrated in the body fluids. Examination of the chyle from the thoracic duct of dogs constitutes the simplest method of detecting such particles (Volkheimer, 1964).

III. Determination of the Rate of Persorption

The rate of persorption depends on several factors. In addition to the amount of the substance present, an important role is played by the motion of the mucosa of the digestive tract, particularly that of the muscularis mucosae.

The rate of persorption can be measured quantitatively. Reproducible results are given by the methods described in the following, for which starch granules are again a very suitable material.

A. Methods

After hemolysis, the blood sample is centrifuged several times. The sediment obtained is then mounted between slides and examined under the microscope. The various kinds of particles present are counted separately. Starch granules are identified under polarized light. Reproducible results are obtained only when the whole sediment is thoroughly examined, an excessively time-consuming procedure. Apart from this, very special precautions must be taken to exclude any possibility of contamination. Here again a great deal of time is taken up by the necessary control tests.

When starch granules are used as the model in these quantitative tests, it is absolutely essential that the bloodstream be free from nutritional starch granules before tests are started. To attain this end, it is sufficient to avoid the ingestion of any food containing starch for 3 days. Granule size distribution and particle counts obtained in tests carried out mainly with cornstarch and potato starch are shown in Table I and Fig. 1.

TABLE I

DIAMETER AND NUMBER OF STARCH GRANULES IN CORNSTARCH AND POTATO STARCH

Starch variety	Granule diameter (μm)	No. granules in 1 gm	No. granules in 200 gm
Cornstarch	3–25	240×10^6	48×10^9
Potato starch	5–110	12×10^6	2.4×10^9

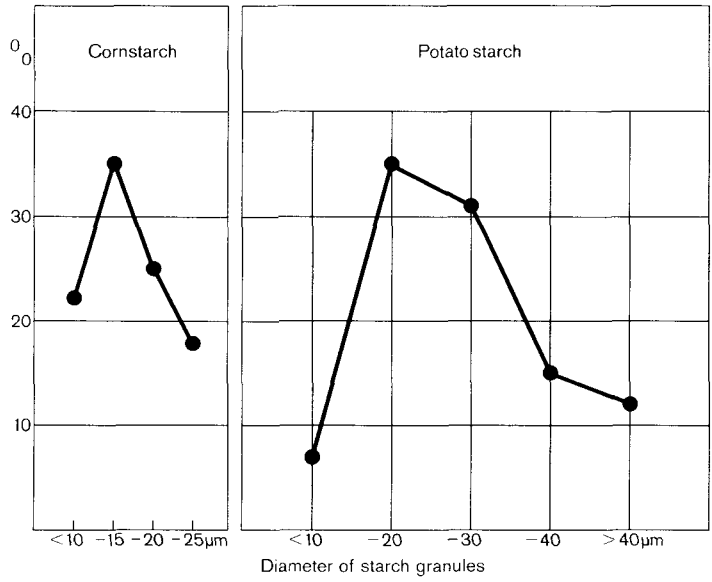

FIG. 1. Size distribution of cornstarch and potato-starch granules.

B. PERSORPTION RATES IN ANIMALS

Starch grains can always be found in the venous blood of animals fed with cereals. The granules disappear from the blood only after 3 days on a starch-free diet.

1. *Detection of Persorbed Starch Granules in Chickens*

a. Chickens (n = 4) were kept for 3 days on a starch-free diet, after which starch granules were no longer present in the venous blood. Then,

using gastric intubation, 20 gm cornstarch (= 4.8×10^9 starch granules) was applied orally. This was followed by taking 1-ml blood samples from the wing veins at 0.5-hour intervals. Cornstarch granules were found to be present in all the samples. The mean values are shown in Fig. 2A. The peak value was reached after 60 minutes.

b. Chickens (n = 4) were fed cereals, the last feed being given on the evening prior to the test. In the morning, a 1-ml venous blood sample was taken, followed by the application of 20 gm cornstarch by stomach tube. Further 1-ml venous blood samples were then taken at 0.5-hour intervals. Starch granules were found in all the samples. The mean values are shown in Fig. 2B. The peak value was reached after 60 minutes.

c. Chickens (n = 4) were fed cereals and a 1-ml venous blood sample taken shortly after feeding. This was followed by the application of 20 gm cornstarch by gastric tube, after which 1-ml venous blood samples were taken at 0.5-hour intervals. Starch granules were present in all the samples. The mean values are shown in Fig. 2C. The peak value was reached after 60 minutes.

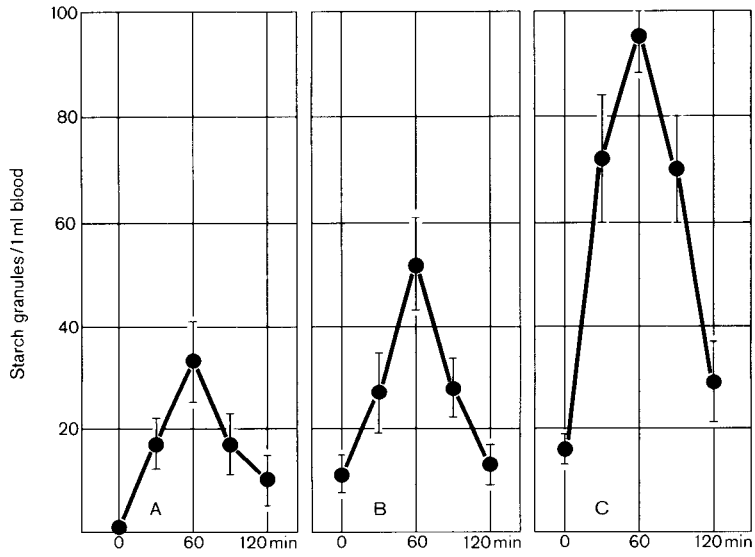

FIG. 2. Starch granules in the venous blood of chickens after oral application of 20 gm cornstarch: (A) starch-free feed for 3 days prior to the test; (B) cereal feed 8 hours before the test; (C) cereal feed immediately prior to the test.

2. *Detection of Persorbed Starch Granules in the Venous Blood of Dogs*

a. Detection of Persorbed Cornstarch Granules. Medium-sized dogs ($n = 4$) were fed 200 gm cornstarch ($= 48 \times 10^9$ starch granules), after which 10-ml venous blood samples were taken at 0.5-hour intervals. Cornstarch granules were detected in all the samples. The mean values are shown in Fig. 3A. The peak value was reached after 2 hours.

b. Detection of Persorbed Potato-Starch Granules in the Venous Blood of Dogs. Medium-sized dogs ($n = 4$) were fed 200 gm potato starch ($= 2.4 \times 10^9$ starch granules) mixed with cream, after which 10-ml venous blood samples were taken at 0.5-hour intervals. Potato-starch granules were detected in all the samples. The mean values are shown in Fig. 3B. The peak value was reached after 1 hour.

C. Persorption Rates in Man

Persorption rates were investigated by means of self-testing with the aid of a large team of medical students of both sexes from the Humbolt University, Berlin. The most important results obtained are described below.

1. *Detection of Persorbed Cornstarch Granules in the Blood*

a. Young (22–26 years of age) test subjects of both sexes ($n = 4$) drank a suspension of 200 gm cornstarch ($= 48 \times 10^9$ starch granules) in buttermilk, after which 10-ml venous blood samples were taken from them at 2-minute intervals, time being reckoned from the first swallowing. Cornstarch granules were detected in all the samples. The mean values are shown in Fig. 4A. The peak value was reached after 6 minutes.

b. Young test subjects ($n = 4$) drank a suspension of 200 gm cornstarch, after which 10-ml venous blood samples were taken at 0.5-hour intervals. Cornstarch granules were found in all samples. The mean values are shown in Fig. 4B. The peak value was reached after 90 minutes.

c. Young test subjects ($n = 4$) drank a suspension of 200 gm cornstarch, after which 10-ml venous blood samples were taken at intervals of 4 hours. Cornstarch granules were found in all samples. The mean values are shown in Fig. 4C. The starch granules had almost completely disappeared from the blood after 24 hours.

2. *Detection of Persorbed Potato-Starch Granules in the Blood*

a. Young test subjects ($n = 4$) drank a suspension of 200 gm potato starch ($= 2.4 \times 10^9$ starch granules) in buttermilk, after which 10-ml

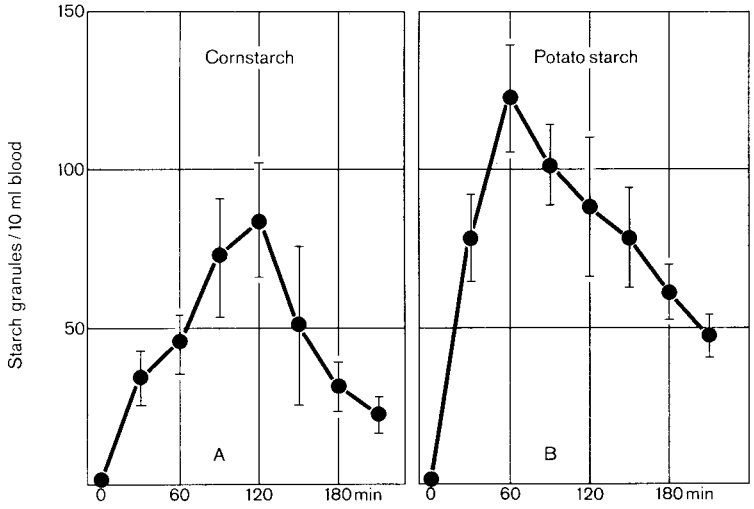

FIG. 3. Starch granules in the venous blood of dogs after a meal of starch: (A) after 200 gm cornstarch (48×10^9 starch granules); (B) after 200 gm potato starch (2.4×10^9 starch granules).

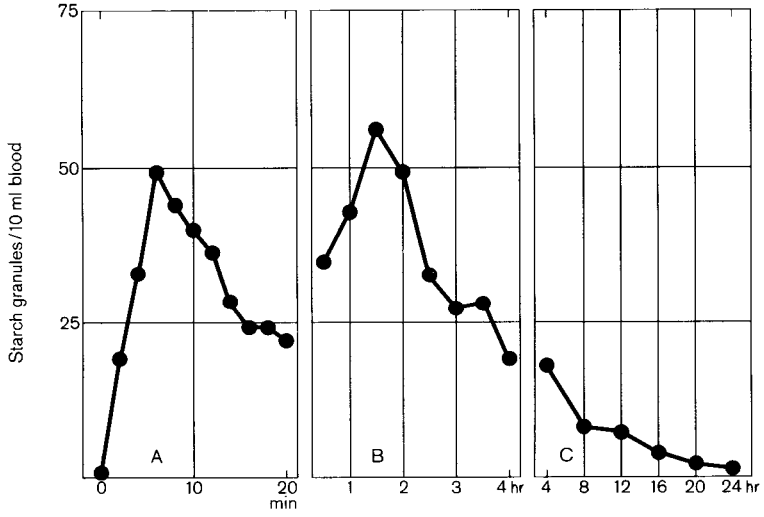

FIG. 4. Cornstarch granules in the venous blood of young test subjects after ingestion of 200 gm cornstarch. A first peak appears 6 minutes after ingestion (A), a second after 90 minutes (B). Only a few isolated starch granules remain in the blood 24 hours after ingestion (C).

blood samples were taken at 5-minute intervals. Potato-starch granules were found in all the samples. The mean values are shown in Fig. 5A. The peak value was reached after 10 minutes.

b. Young test subjects (n = 4) drank a suspension of 200 gm potato starch, after which 10-ml venous blood samples were taken at 0.5-hour intervals. Potato-starch granules were present in all samples. The mean values are shown in Fig. 5B. The peak value was reached after 90 minutes.

3. *Persorption Rates Following Ingestion of Different Numbers of Particles*

a. Cornstarch Granules. Young test subjects (n = 4) drank successive, increasing amounts (50, 100, 200, and 300 gm; 100 gm = 24×10^9 starch granules) of cornstarch in suspension at intervals of 1 week. In the time interval 60–150 minutes after each intake, 10-ml venous blood samples were taken at 0.5-hour intervals. The greater the amount of starch ingested, the larger was the number of cornstarch granules in the blood (Fig. 6A).

b. Potato-Starch Granules. Young test subjects (n = 4) drank successive, increasing amounts (50, 100, 200, and 300 gm; 100 gm = 1.2×10^9

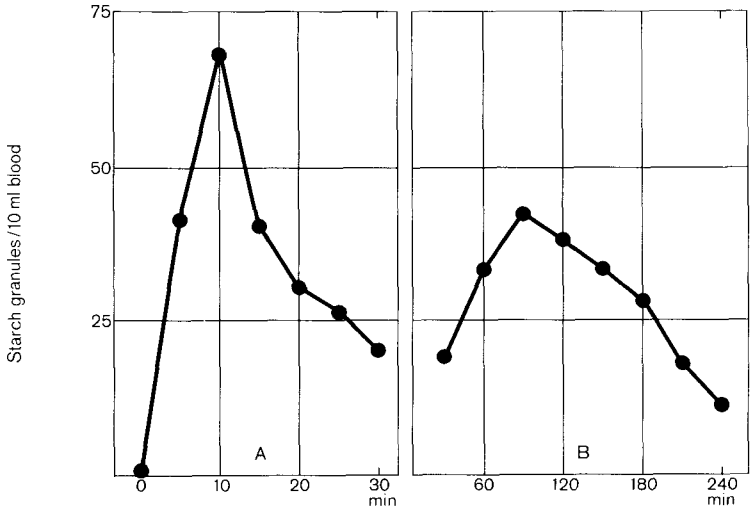

FIG. 5. Potato-starch granules in the venous blood of young test subjects after ingestion of 200 gm potato starch. A first peak appears 10 minutes after ingestion (A), a second after 90 minutes (B).

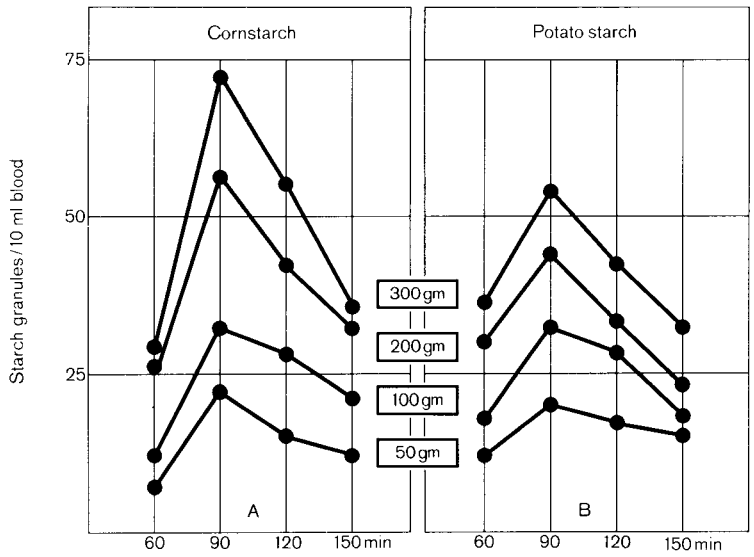

FIG. 6. Starch granules in the venous blood of young test subjects after ingestion of various amounts of starch: (A) after 50, 100, 200, and 300 gm cornstarch; (B) after 50, 100, 200, and 300 gm potato starch.

starch granules) of potato starch in suspension at intervals of 1 week. In the time interval 60–150 minutes after each intake, 10-ml venous blood samples were taken at 0.5-hour intervals. The greater the amount of starch ingested, the larger was the number of potato-starch granules in the blood (Fig. 6B).

4. *Age Differences*

a. In Rate of Persorption of Cornstarch Granules. Young test subjects (n = 4) with an average age of 24 years, together with elderly test subjects (n = 4) with an average age of 72 years, each drank a suspension of 200 gm cornstarch. From 1 to 3 hours after the intake, 10-ml venous blood samples were taken at 0.5-hour intervals. The number of cornstarch granules in the blood was higher in the younger than in the older subjects (Fig. 7A).

b. In Rate of Persorption of Potato-Starch Granules. Young test subjects (n = 4) with an average age of 24 years, together with elderly test subjects (n = 4) with an average age of 72 years, each drank a suspension of 200 gm potato starch. From 1 to 3 hours after the intake, 10-ml venous blood samples were taken at 0.5-hour intervals. The

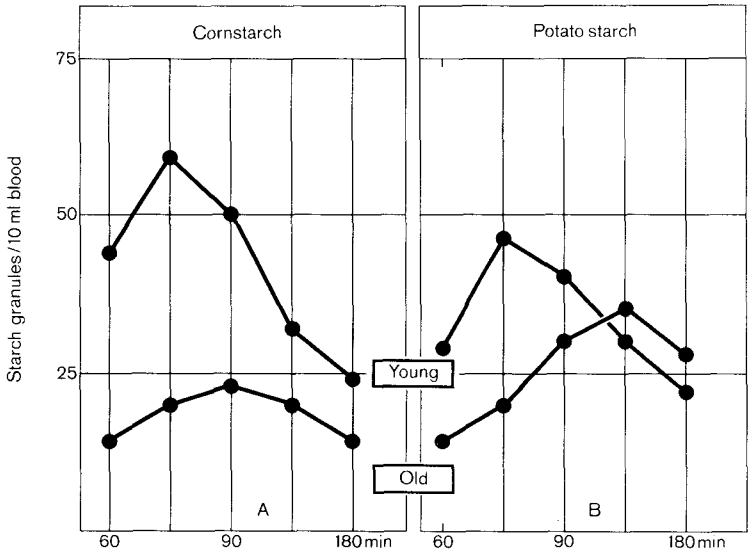

FIG. 7. Comparison of persorption rates in young and old test subjects after ingestion of 200 gm cornstarch (A) and after ingestion of 200 gm potato starch (B).

number of potato-starch granules in the blood was at first higher in the younger than in the older subjects. (Fig. 7B). This relationship was, however, reversed at 120 minutes after intake.

5. *Persorption during Sleep*

a. Young test subjects (n = 4) drank a suspension of 200 gm cornstarch during the morning, after which 10-ml venous blood samples were taken at 1-hour intervals. One week later the test was repeated during physiological night sleep after the subjects had taken the same amount of starch late in the evening before going to bed. A cannula had previously been inserted in the cubital vein. During sleep, the subject's partner took 10-ml venous blood samples at 1-hour intervals. The mean values of the numbers of starch granules found are shown in Fig. 8A. The number of persorbed starch granules in the blood is noticeably higher during sleep than during the day.

b. Young test subjects (n = 4) carried out the same test using 200 gm potato starch. The mean values of the numbers of starch granules (Fig. 8B) likewise revealed a noticeably higher rate of persorption during sleep.

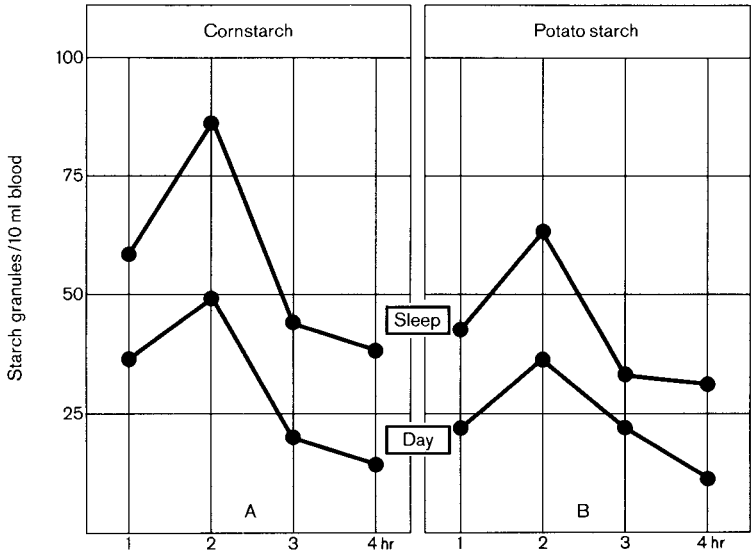

FIG. 8. Comparison of persorption rates during the day and during sleep after ingestion of 200 gm cornstarch (A) and after ingestion of 200 gm potato starch (B).

IV. Modification of Persorption Rates

A. Effect of Drugs on Persorption Rates

1. *Increase in the Persorption Rate*

a. Effect of Neostigmine. As in the tests already described, young test subjects ($n = 4$) drank a suspension of 200 gm cornstarch. One week later the test was repeated with the simultaneous application of 0.5 mg neostigmine by subcutaneous injection. The rate of persorption was noticeably higher under neostigmine (Fig. 9A).

b. Effect of Caffeine. As in the tests already described, young test subjects ($n = 4$) drank a suspension of 200 gm cornstarch. One week later the test was repeated with the simultaneous application of 200 mg caffeine by subcutaneous injection. The rate of persorption was noticeably higher under caffeine (Fig. 9B).

c. Other Drugs. Similar tests to the foregoing demonstrated a noticeable increase in the persorption rate after application of the following drugs: metoclopramide, 10 mg by intramuscular injection; papaverine,

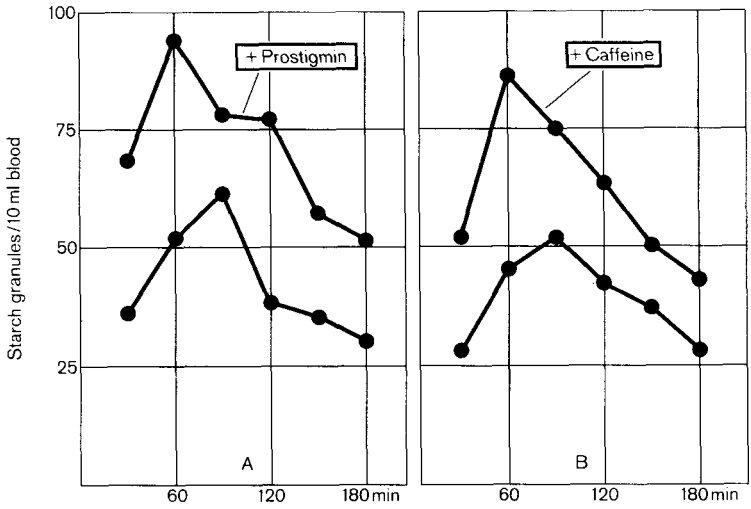

FIG. 9. Effect of drugs on the persorption rate: both (A) neostigmine (Prostigmin) and (B) caffeine increase the rate.

100 mg by intramuscular injection; castor oil, 20 gm per os; polygalacturonic acid, per os (30 gm Solcoray; Solco Basel, AG).

2. *Decrease in the Persorption Rate*

a. Effect of Atropine. Young test subjects (n = 4) drank a suspension of 200 gm cornstarch. One week later the test was repeated with the simultaneous application of atropine (0.01 mg/kg body weight). The rate of persorption was noticeably lower under atropine (Fig. 10A).

b. Effect of Barbituric Acid. Young test subjects (n = 4) drank a suspension of 200 gm cornstarch. One week later the test was repeated with the simultaneous application of barbituric acid (250 mg per os). The rate of persorption was noticeably lower under barbituric acid (Fig. 10B).

c. Effect of Detergents. A marked reduction in the rate of persorption was also observed when 10 gm of Tween 20 was added to the starch suspension. This effect was even greater when Tween 80 was added.

B. Effects of Coffee Drinking and Smoking

1. *Effect of Coffee on Persorption of Cornstarch Granules*

Young test subjects (n = 4) drank a suspension of 200 gm cornstarch immediately after consuming coffee prepared in the usual way from 20

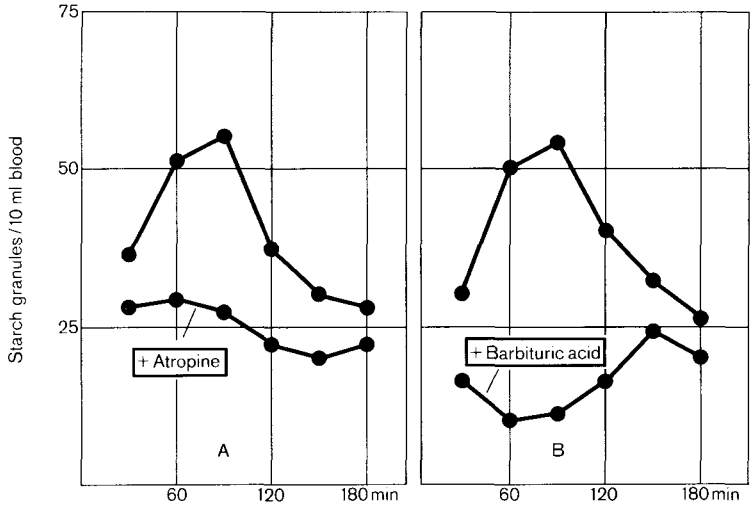

FIG. 10. Effect of drugs on the persorption rate: both (A) atropine and (B) barbituric acid reduce the rate.

gm ground coffee beans (caffeine content 228 mg). Then, 10-ml venous blood samples were taken at 0.5-hour intervals. For comparison, the test was repeated after 1 week without the consumption of coffee. The mean values for persorbed starch granules (Fig. 11A) revealed a marked increase in the rate of persorption under the action of coffee.

2. *Effect of Coffee on Persorption of Potato-Starch Granules*

In similar tests in which young subjects ($n = 4$) drank a suspension of 200 gm potato starch, the simultaneous consumption of coffee (20 gm, caffeine content 228 mg) was again seen to cause a marked increase in the rate of persorption (Fig. 11B).

3. *Caffeine-Free Coffee*

Further tests similar to the foregoing showed that caffeine-free coffee did not cause any increase in the rate of persorption of starch granules.

4. *Nicotine*

A large number of comparative tests were carried out to investigate the effect of nicotine on the rate of persorption. It was found that continuous cigarette smoking increased the rate of persorption on the average by 30%.

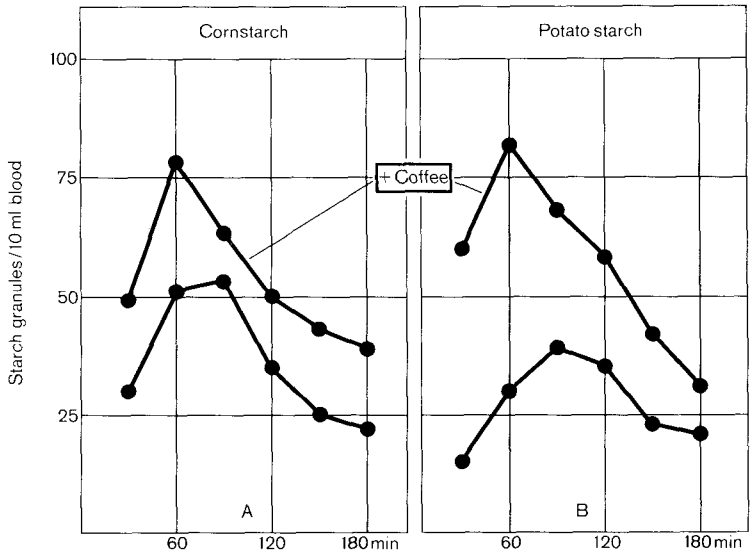

FIG. 11. Effect of coffee on the persorption rate. Simultaneous drinking of coffee (caffeine content 228 mg) increases the rate. Observations were made following ingestion of 200 gm cornstarch (A) and of 200 gm potato starch (B).

V. Excretion of Persorbed Particles

Several factors are involved in the elimination of particles from the blood circulation. One of these is the temporary embolism of smaller vessels prior to removal of the particles from the vascular system [see Volkheimer (1972), pp. 61 and 70].

A. Urinary Excretion

1. *Quantitative Tests*

a. Excretion of Cornstarch Granules. Young tests subjects ($n = 4$) drank a suspension of 200 gm cornstarch, after which each of them emptied the urinary bladder completely at 1, 2, 3, 4, and 8 hours. The average number of cornstarch granules excreted during this 8-hour period was 124. The percentage distribution of the separate fractions is shown in Fig. 12A.

b. Excretion of Potato-Starch Granules. Young tests subjects ($n = 4$) drank a suspension of 200 gm potato starch, after which each of them

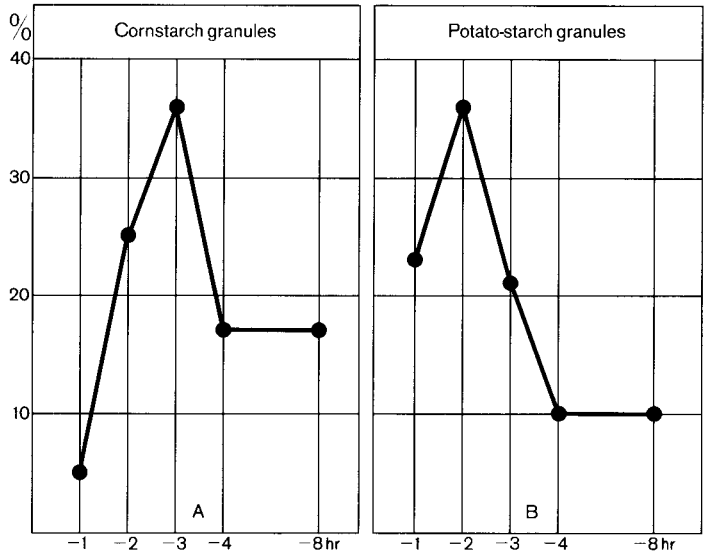

FIG. 12. Excretion (%) of persorbed starch granules in the urine after ingestion of 200 gm cornstarch (A) and of 200 gm potato starch (B). Urinary fractions collected at 1, 2, 3, 4, and 8 hours after ingestion were examined.

emptied the urinary bladder completely at 1, 2, 3, 4, and 8 hours. The average number of potato-starch granules excreted during this 8-hour period was 79. The percentage distribution of the separate fractions is shown in Fig. 12B.

2. *Granule Size Distribution*

a. Cornstarch Granules (diameter 3–25 μm). Young test subjects (n = 4) drank a suspension of 200 gm cornstarch, after which a venous blood sample was taken every hour for 3 hours, hemolyzed, and centrifuged. At the same time the urine spontaneously discharged at hourly intervals was collected and centrifuged. The sizes of the cornstarch granules in the blood and urine were measured and compared with those of the native starch granules as shown in Fig. 13.

b. Potato-Starch Granules (5–110 μm). Young test subjects (n = 4) drank a suspension of 200 gm potato starch, after which a venous blood sample was taken every hour for 3 hours, hemolyzed, and centrifuged. At the same time the urine passed spontaneously at hourly intervals was collected and centrifuged. The sizes of the potato-starch granules in the blood and urine were measured and compared with those of the native starch granules (see Fig. 14).

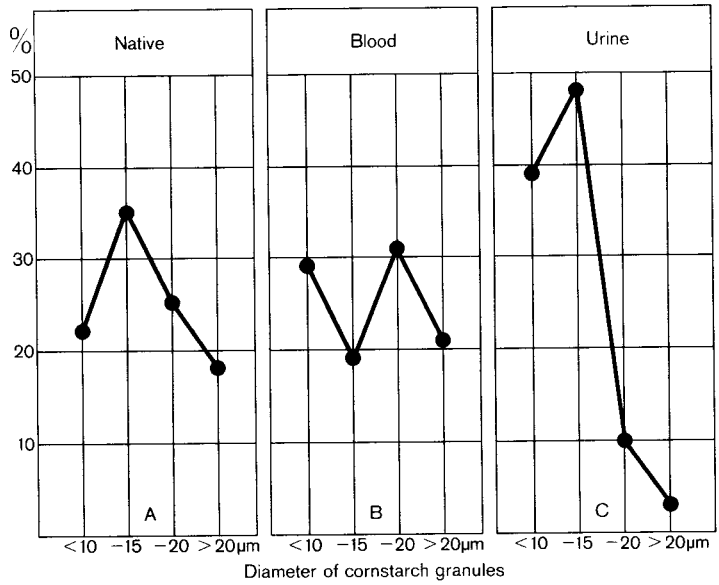

FIG. 13. Size distribution (%) of cornstarch granules in blood and urine compared with that of native starch.

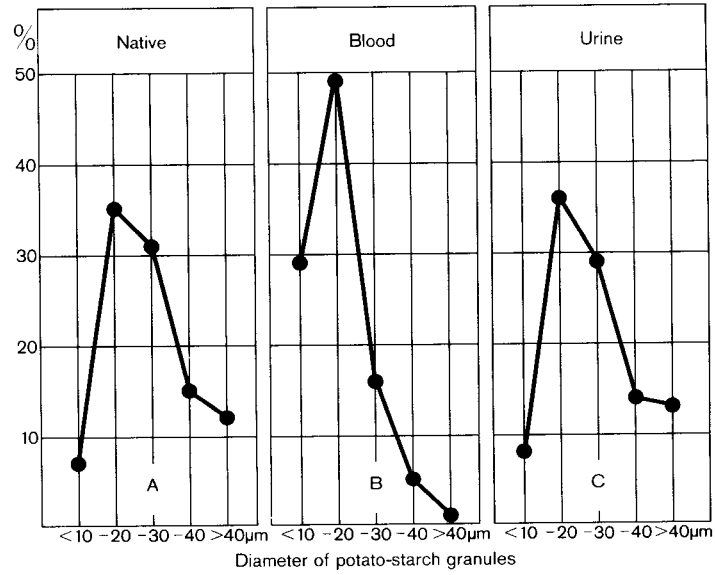

FIG. 14. Size distribution (%) of potato-starch granules in blood and urine compared with that of native starch.

3. *Effect of Drugs*

a. Caffeine. Young test subjects ($n = 4$) drank a suspension of 200 gm potato starch. In the 8-hour urine subsequently collected, the average number of potato-starch granules counted was 66. One week later the test was repeated with the simultaneous application of 200 mg caffeine per os. The average number of potato-starch granules in the subsequent 8-hour urine was 178.

b. Diuretics. Comparative observations made under the simultaneous action of furosemide (40 mg given intravenously) and, in separate tests, of hydrochlorothiazide (75 mg per os) revealed a considerable increase in the amount of urine passed but no significant change in the rate of excretion of the persorbed starch granules.

B. Biliary Excretion

1. *Cornstarch Granules*

A few days after cholecystectomy—with T-drain *in situ*—cooperative cholecystectomized patients ($n = 4$) drank a suspension of 200 gm cornstarch in cold tea. The bile discharged via the T-drain was then collected in 10-minute fractions for 1 hour. The number of cornstarch granules in the bile was counted and the average number per 1 ml bile calculated. The results are shown in Fig. 15A. By means of X-ray film tests, the bile was shown to be free of trypsin, i.e., there was no reflux discharge from the duodenum.

2. *Potato-Starch Granules*

A few days after cholecystectomy—with T-drain *in situ*—cooperative cholecystectomized patients ($n = 4$) drank a suspension of 200 gm potato starch. The bile discharged via the T-drain was then collected in 10-minute fractions for 1 hour. The number of potato-starch granules in the bile was counted and the average number per 1 ml bile calculated. The values are shown in Fig. 15B.

C. Other Excretory Routes

Similar tests were carried out to study the elimination of persorbed particles in breast milk and cerebrospinal fluid as well as their diaplacental passage. Quantitative measurements of these routes were also made. The mechanism by which persorbed particles pass from the pulmonary vessels into the alveolar lumen was investigated with the aid of histological sections (Volkheimer, 1972, p. 65).

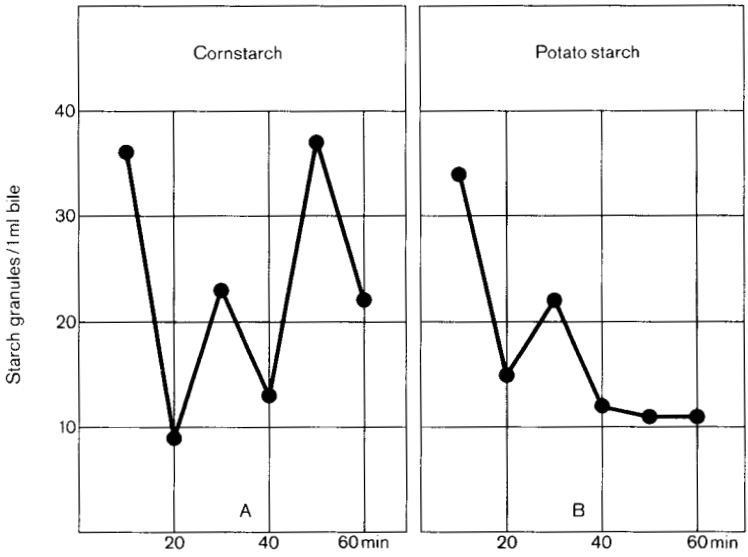

FIG. 15. Excretion of persorbed starch granules in the bile after ingestion of 200 gm cornstarch (A) and of 200 gm potato starch (B).

VI. Breakdown of Persorbed Particles

The relatively rapid clearance of persorbed particles from the blood cannot be explained solely by their elimination from the vascular system. A further factor involved in the disappearance of particles from the circulation and other organs is their breakdown, a process in which both enzymes and phagocytosis play an important part.

A. Enzymic Breakdown

Favorable sites for observing the enzymic breakdown of particles are the serous cavities of the body.

1. *Enzymic Breakdown in the Peritoneal Cavity*

Considerable structural changes were shown by some of the starch granules present in fluid used to rinse out the peritoneal cavity of laboratory animals fed potato starch. These changes are of the same kind as those seen in starch grains introduced directly into the peritoneal cavity. Larger potato-starch granules undergo more rapid breakdown than smaller ones.

2. *Enzymic Breakdown in the Cerebrospinal Fluid*

a. In Dogs. Twenty-four hours after feeding potato starch to dogs, potato-starch granules showing considerable structural changes could be seen in the cerebrospinal fluid. The structural changes were of the kind occurring in enzymic breakdown of starch granules.

b. In Man. Volunteer patients in whom lumbar puncture had to be carried out for diagnostic reasons drank a suspension of potato starch 24 hours beforehand. Some of the potato-starch granules found in the cerebrospinal fluid sediment showed marked structural changes similar to those occurring in enzymic breakdown.

B. Phagocytosis

1. *Model Substance*

Rice-starch granules, which have a diameter of 2 to 10 μm, are very suitable for phagocytosis tests.

2. *Phagocytosis in the Spleen*

Dogs fed rice starch were subjected to splenectomy at varying intervals after feeding. Smears were prepared from the cut surface of the spleen and stained. A few phagocytized rice-starch granules were visible in macrophages and microphages (Volkheimer, 1972, 1974).

3. *Phagocytosis in the Liver*

Small laboratory animals were given potato starch by the enteral route. At varying intervals the liver was excised and examined histologically. A few potato-starch granules surrounded by phagocytizing cells could be seen in the sinusoids and interlobular veins.

4. *Effect of Aristolochic Acid*

Aristolochic acid is used therapeutically as an activator of phagocytosis. Young tests subjects ($n = 4$) drank a suspension of 200 gm rice starch ($= 160 \times 10^9$ starch granules), after which 1-ml venous blood samples were taken at 0.5-hour intervals and the number of rice-starch granules counted. The test was repeated after 1 week when the subjects had been under medication with aristolochic acid for 3 days at an oral dosage of 0.45 mg/day. Ninety minutes after ingestion of the rice starch, the average numbers of rice-starch granules in the blood in the two sets of tests differed significantly (Fig. 16). No differences were detectable among the blood samples taken at other times.

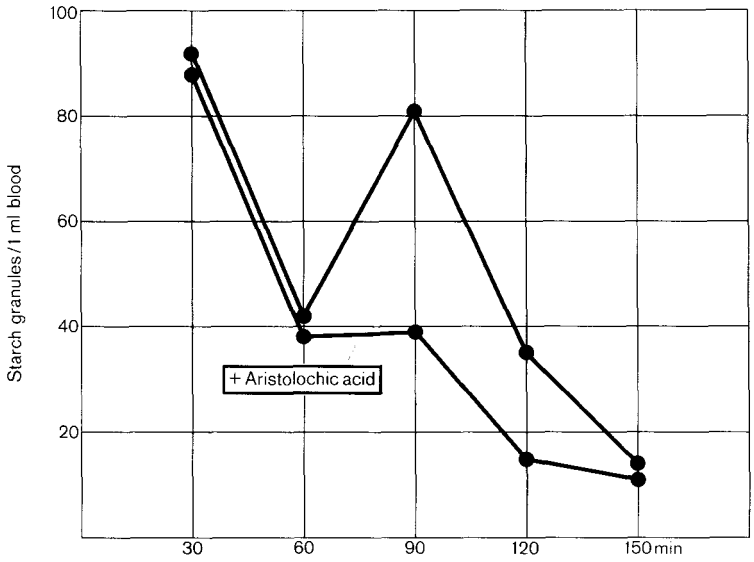

FIG. 16. Rice-starch granules in the venous blood of young test subjects after ingestion of 200 gm rice starch (160×10^9 rice-starch granules). Premedication with aristolochic acid suppresses the second rise in the number of granules at 90 minutes after ingestion.

VII. Discussion

Persorption of solid particles in the micrometer size range is a fact. The observations described in this review effectively disposed of any doubt that such large particles were capable of passing through the intestinal mucosa. The question whether persorption is a "physiological" or "pathological" process remains a purely academic one.

Absorption of a particle of this size by the enterocyte body can be ruled out: many of the persorbed particles have a far larger diameter than the frontal aspect of the enterocyte that is directed toward the lumen. Paracellular passage between the enterocytes has been demonstrated as the mechanism of persorption.

Actually, the closely interlocked enterocyte layer (the so-called tight junction) forms a fairly impenetrable barrier to passage of particles in this way. The only interruption in this network of tight junctions is that due to goblet cells. In fact, as examination under the electron scanning microscope reveals, a loosening of the tight junctions of the intestinal mucosa occurs in the immediate neighborhood of the goblet cells. Spontaneous loosening is also possible as a result of cell desquamation.

Histological sections studied in our laboratory have often revealed the passage of particles through the mucosa in a desquamation zone, namely at the tips of the intestinal villi (Volkheimer, 1972). A further possibility for the passage of particles is offered by mechanical lesions of the tight junctions around the bases of the tightly packed villi due to the entry between them of large particles. The result is a mechanical loosening of the tight junctions that is exacerbated by two factors: (*1*) the rhythmic contraction of the villi and (*2*) the rhythmic hammering action of the vascular pulsation, which is transmitted to the mucosa.

The assumption that mechanical factors are responsible for the "kneading" of particles through the epithelial cell layer finds support in the observation that the rate of persorption is affected by changes in the movements of the villi brought about by drugs. When the movements of the villi are stimulated by neostigmine or caffeine, the rate of persorption increases, but when it is slowed down by atropine or barbituric acid, the rate decreases. In the case of caffeine, there is also the possibility that the increase in the rate of persorption is potentiated by the intensification of vascular pulsation induced by this substance.

Primary removal of persorbed particles from the mucosa occurs by two routes—via the chyle and via the portal circulation. The proportions transported in these two ways have not so far been determined, although it seems likely that smaller particles are carried mainly by the portal circulation, and larger ones mainly by the chyle. Particles transported by the *chyle* first pass via the thoracic duct into the pulmonary circulation, where they may cause temporary embolism of small pulmonary vessels. After a short time they are eliminated by passage into the alveolar lumina (Volkheimer, 1972). Many particles, including larger ones, also reach the pulmonary circulation, however, via vascular anastomoses. Particles transported by the *portal circulation* may bring about temporary embolism of hepatic vessels (Volkheimer, 1972). The excretion of particles in the bile can be measured quantitatively.

The *rate of persorption*, which is derived from the number of particles counted in the peripheral blood, furnishes only a *relative* measure of the actual number of persorbed particles. Many of the factors here involved must first be disregarded since neither their quantitative effect nor chronological course is determinable. Account must also be taken of the very extensive surface area—extending from the cardia to the rectum—over which persorption occurs. Among the nonquantifiable factors involved are temporary embolisms and the breakdown, phagocytosis, distribution, and excretion of the particles.

No automatic method of counting persorbed particles in the blood has yet been devised. The method of counting used in these studies is not

only very tedious but excessively time-consuming. To count the particles in 10 ml of blood, a fairly experienced operator requires about 5 hours. It is essential that the whole of the sediment is examined if important findings are not to be missed: a superficial examination reveals nothing. In the studies reported here, a standard amount of 200 gm starch was adopted. Clearly, however, 100 gm would also be adequate to give valid results.

The *persorption ratio* can be roughly estimated at 1:50,000 (±50%). This means that 1 out of about every 50,000 ingested particles capable of persorption will be persorbed. In spite of this low ratio, an astonishingly large number of persorbed particles circulate in the blood. Here the decisive factor is the enormous quantity of persorbable particles made available by conventional foodstuffs (Volkheimer, 1972).

In the experiments carried out to measure the rate of persorption, it was noticeable that the first particles appeared in the peripheral blood only a few seconds after ingestion of the test substance. The number of particles in the blood attains a first maximum after a few minutes. It then falls, only to rise again after a short time to a second peak value at about 100 minutes after ingestion. In many other tests, a third maximum was observed at about 210 minutes after ingestion. The precise causes of these two or even three peaks in the numbers of particles are unknown.

VIII. Future Developments

The immunological significance of the persorption phenomenon is obvious. Preliminary studies in the microangiological and experimental gerontological fields have yielded interesting results, in particular the destruction of small vascular areas in the region of the CNS as a result of embolism by persorbed particles. Since PVC particles and asbestos fibers undergo persorption in the small intestine, the phenomenon acquires importance in the field of environmental protection. Its heuristic possibilities are still, however, a long way from being exhausted.

IX. Conclusion

Persorption is an extremely interesting phenomenon whose full implications will be revealed only when much further work on the problem has been done. The aim of this brief review of the fundamental studies so far undertaken has been to make it known to a wider scientific circle and to stimulate interest in further research.

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