

THE PHENOMENON OF PERSORPTION: PERSORPTION, DISSEMINATION, AND ELIMINATION OF MICROPARTICLES

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SUMMARY

Solid microparticles, whose diameter lies far in the micrometer range (μm), such as pollen, spores, starch-granules, cellulose particles, silicates, crystals, diatoms, soot particles and other natural and industrial dusts are regularly incorporated in a noteworthy quantity in the alimentary tract. Their paracellular translocation through transitory leaks in the epithelial cell layer has been confirmed. Mechanical factors play an important role here: The solidity of the microparticles, the constantly hammering vascular pulsation communicated to the mucosa and the motility of the muscularis propria and muscularis mucosae are causal factors for the loosening of tight junctions and for the appearance of leaks in the epithelial cell layer. The microparticles are transported from the sub-epithelial region through lymph tracts via the thoracic duct but also through veins and disseminated with the blood stream. They are to be found in the peripheral blood already within a few minutes of peroral application.

There are numerous ways in which the microparticles can be eliminated from the blood stream. Their passage into the alveolar lumen, bile, urine, cerebrospinal fluid, peritoneal cavity, through the lactating mamma into the milk and also the transplacental transfer to the foetal blood circulation has been observed. Numerous ready-to-serve foods contain large quantities of solid microparticles capable of persorption.

INTRODUCTION

The enteral uptake of microparticles was observed for the first time in 1844 and subsequently confirmed on several occasions. However, it was not considered credible and little notice was taken of it. The term microparticle designates solid particles of a diameter less than $1/10^{\text{th}}$ of a millimetre. Under the working title of "Persorption", this phe-

nomenon of the enteral translocation of solid microparticles and the question of where persorbed particles end was investigated in detail between 1959 and 1967 in the laboratories for experimental gastroenterology of the 1st Medical Clinic (Charité) of the Humboldt University, Berlin.

HISTORY

The enteral permeability for microparticles has been known for more than 150 years. *Herbst* gave a starch infusion to a female dog and three hours later found starch-granules in the chyle and in the blood. *Oesterlen* demonstrated some of the charcoal particles fed to chicken and rabbits in their blood: "Above all, I must indeed excuse myself for having thought at all of the possibility of solid, undissolved substances passing from the intestinal mucosa into the blood and of even carrying out experiments on this". *Eberhard* found charcoal particles fed to rabbits in the chyle and in the blood and also sulphur crystals fed to dogs in the chyle. *Donders* and his post-graduate student

Mensonides found charcoal particles and starch-granules from the food fed to them in the mesenteric blood of the frog and rabbit. *Moleschott* had his assistant *Marfels* feed frogs with pigment particles and sheep erythrocytes, which they were then able to demonstrate in the blood. *Virchow* made the following comment on all this: "There has been much talk recently about the absorption of solid bodies. I cannot understand how this penetration of solid bodies can be called absorption or even resorption. In all these cases, it is a question of a mechanical perforation, a coarse form of permeability, a dissociation by the solid body. Should this be called absorption?". He subsequently considered

Figure 1:

- a. E.F. Gustav HERBST (1803-1893), Göttingen, finds starch-granules in the chyle and blood three hours after administering starch flour to a dog (1844).
- b. Franz Cornelis DONDERS (1818-1889), Utrecht, and his post-graduate student MENSONIDES find charcoal particles and starch-granules fed to frogs and rabbits in the mesenteric blood (1846, 1851)
- c. Rudolf KOELLIKER (1817-1905) and Rudolf VIRCHOW (1821-1902) in Würzburg 1850. Koelliker's post-graduate student EBERHARD demonstrates charcoal particles fed to rabbits in the chyle and blood. He finds sulphur crystals fed to dogs in the chyle (1847, 1851). VIRCHOW believes that this is due to a mechanical perforation of epithelial layer (1852, 1854).
- d. Jakob MOLESCHOTT (1822-1893), Heidelberg and his assistant MARFELS find pigments and sheep cells fed to frogs in the blood of the frogs (1854)
- e. Rahel HIRSCH (1870-1953), Berlin finds occasional starch-granules after the ingestion of starch flour in the urine and blood of dogs and, for the first time, also in man (1906). When she reports these results in the "Society of the Charité Physicians", she is greeted with laughter.
- f. Fritz VERZÁR (1886-1979), Budapest confirms the results of Rahel HIRSCH on mammals and man (1911). At the Institute for Experimental Gerontology in Basle, he subsequently concerns himself with the cell disintegration of the intestinal epithelium. In 1969, he discusses with VOLKHEIMER the influence of motor factors ("villous pump") on the persorption mechanism in the small intestine.
- g. Theodor BRUGSCH (1878-1962), Berlin, Director of the 1st Medical University Clinic of the Charité, formerly the co-assistant of Rahel HIRSCH, recalls in 1956 her studies on the demonstration of starch-granules in urine.
- h. Friedrich Horst SCHULZ (1915-1982), Berlin, the successor of Brugsch, generously encourages the studies of the persorption of microparticles taken up again by VOLKHEIMER in 1959 in the Laboratories for Experimental Gastroenterology at his clinic.



a



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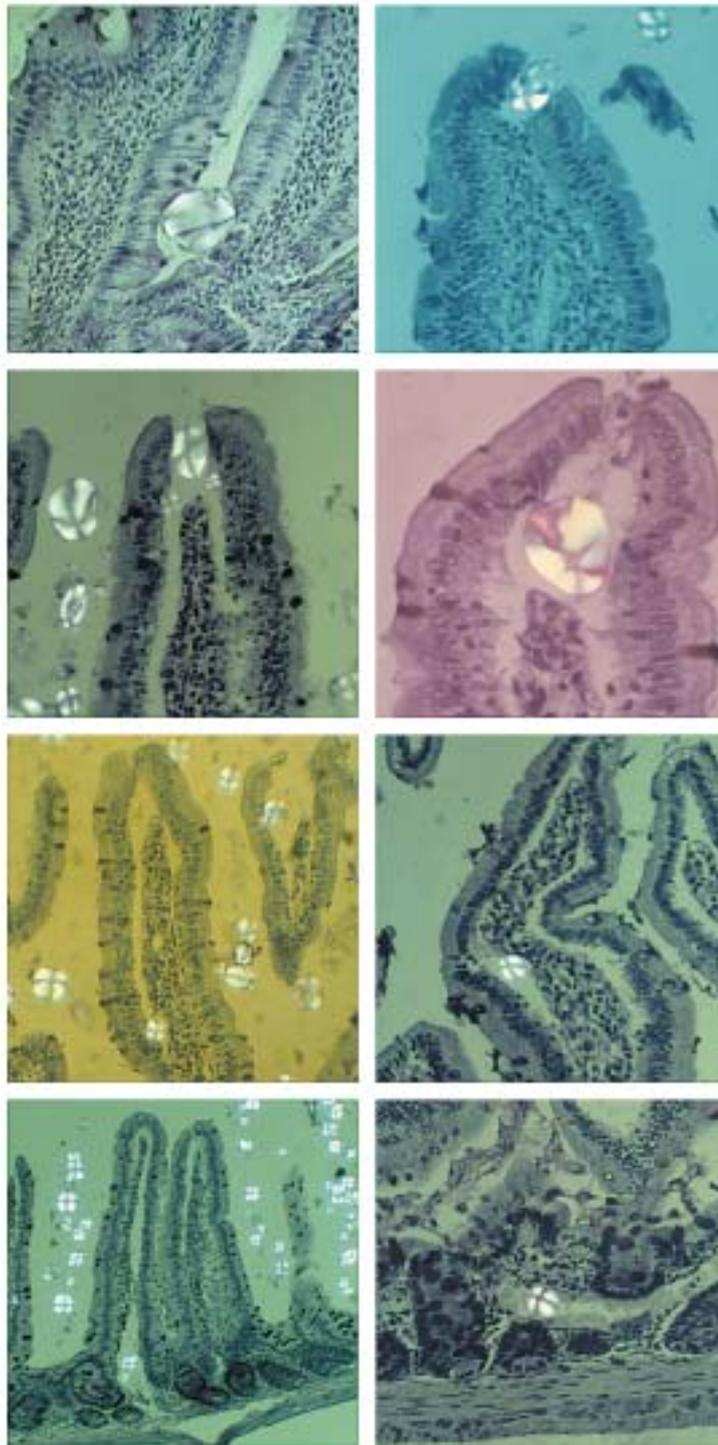


Figure 2: Reconstruction of the persorption process in rats after the ingestion of potato starch. Jejunum and colon. Starch-granules between enterocytes, in the subepithelial region and in the lumen of lymph vessels.

that “the passage of solid parts through the intestinal serosa and into the blood vessels, the so-called resorption of solid parts (*can*) be called at most a perforation of the soft parts”.

In 1906, *Rachel Hirsch* administered starch to dogs and volunteers. She found starch-granules of the kind applied in each case in the blood and in the urine. She noted that “The identification of it would appear to be far less difficult than its acknowledgement.” *Verzár* checked her results: “I must acknowledge that I was certainly prejudiced and indeed approached this question with the very greatest scepticism. Yes, I admit that I was totally convinced of the

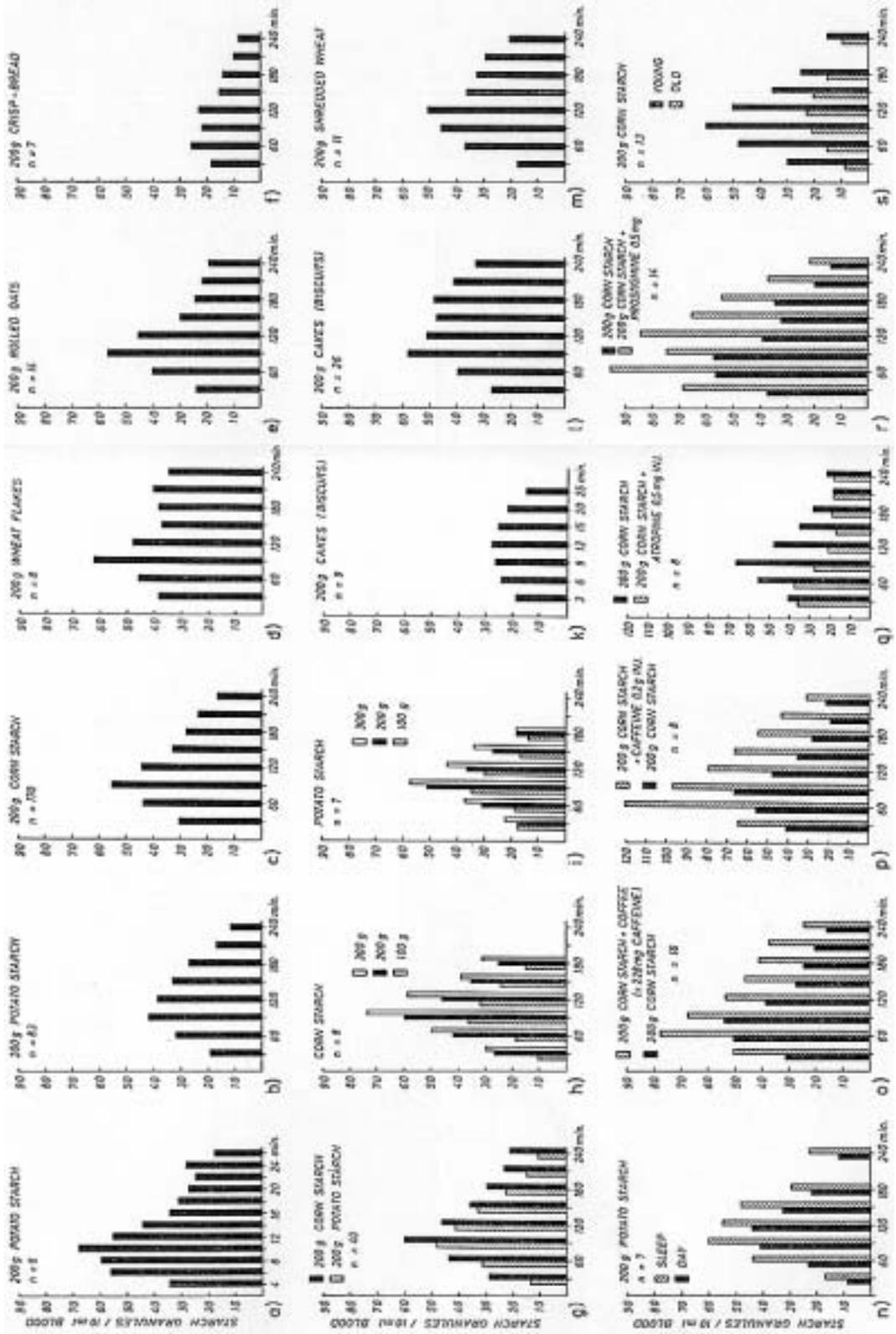
impossibility of this assertion. I thought of two possibilities. Either the granules observed were not starch-granules ... or, however, ...the work had not been carried out with absolute cleanliness and the starch-granules were an impurity, had got into the test-tubes and reactions as dust.” After a very careful investigation in which he excluded any possibility of contamination, he considered it, however, “as proved in confirmation of the details given by *R. Hirsch* that starch-granules as such pass from the intestine into the blood stream and from there can be excreted via the kidneys in the urine” (Figure 1).

RESULTS

For the demonstration of the persorption process, starch-granules of a diameter of 5 to 110 μm are very suitable as model bodies and can be given with the food in generous quantities. In histological sections, they can be identified under the polarising microscope. After starch suspensions are fed to vertebrates, occasional starch-granules can be identified histologically between enterocytes. Others lie in the subepithelial region and many in the lymph vessels of mucosa, submucosa and mesenterium. This shows that the penetration mode for solid microparticles is the paracellular passage through the epithelial cell layer. The upper diameter limit for the persorption capacity was determined: In the chyle of mammals after they had been fed with particles of quartz, it was only very seldom that particles greater than 130 μm were found whereas particles of a diameter of up to 70 μm were frequently observed. Using the same method, microparticles such as pollen, spores, plant cells, diatoms, ground wood pulp, cellulose-

particles, pulverised crab and lobster shells, lyophilised muscle fragments, PVC particles, iron powder, parasite eggs, hair fragments, asbestos fibres, soot and charcoal-particles, silicates and crystals can be found in the chyle (Figure 2).

This phenomenon was also quantitatively observed in self-experiments with a large team of colleagues and medical students. After native starch has been taken, starch-granules can be demonstrated in the venous blood already 100 seconds later. Their number displays a multi-peak characteristic with peaks at about 10, 100 and 210 minutes after the ingestion of particle suspensions. The persorption rate is dependent on the quantity of particles offered. The motility of the muscularis mucosae, drugs, circadian rhythm, age, caffeine and nicotine influence the absorption rate. Other microparticles of a comparable size such as cellulose particles, pollen and lycopodium spores are also found in the venous blood of volunteers after oral application (Figure 3).



On elimination, degradation and temporary deposition

Several possibilities for the elimination of persorbed microparticles from the circulation of the blood were observed: Microparticles of a size capable of causing embolism are arrested in small vessels. The transfer of embolising microparticles into the alveolar lumen can be histologically demonstrated at alveolar vessels. The elimination in the bile was quantitatively determined; it commences already within a few minutes of oral application. Comparable with this is the elimination in the urine after the embolisation of glomerular vessels. This can likewise be quantitatively determined: After the administration of 200 g starch to volunteers, about 100 starch-granules were excreted within 8 hours with the urine, most of this already in the first 4 hours. When caffeine is administered at the same

time, the number of starch-granules found in the urine is almost three times higher whereas there is no significant change in the elimination rate under the influence of diuretics. The elimination through the lactating mamma and into the milk, cerebrospinal fluid and via the placenta into the foetal circulation was likewise quantitatively studied. Individual microparticles capable of embolisation are temporarily retained – even for a long time – and deposited in small blood vessels; in the pulmonary interstitium, they are enclosed and incorporated by multinuclear macrophages. Phagocytosis of persorbed starch-granules was observed in the spleen. A phagocytosis of fragments of starch-granules can be histologically demonstrated in the brain. In further series of tests, the fate of microparticle-induced embolisations in the brain was histologically investigated.

Figure 3: Quantitative studies of the rate of persorption of starch-granules given orally to volunteers (medical students at the Charité, Berlin). The number of granules per 10 ml of venous blood was determined at various time intervals.

- a. Within a few minutes following consumption of 200 g of potato starch-granules are found in venous blood. A first maximum is reached after 10 minutes.
- b. A second peak in appearance of starch-granules in blood is observed about 90 minutes after ingestion of potato starch.
- c. Granules in venous blood upon consumption of 200 g of cornstarch.
- d. The persorption rate of starch-granules is relatively high following intake of wheat flakes.
- e. Persorption of particles upon consumption of rolled oats.
- f. Persorption of particles upon consumption of crisp bread.
- g. Administration of 200 g cornstarch and 200 g potato starch and persorption rates in comparison.
- h,i. Consumption of various weights of starch and comparison of persorption rates.
- k. Starch-granules in venous blood few minutes after ingestion of 200 g biscuit.
- l. The persorption rate is relatively high following the consumption of 200 g of biscuit, although this amount contains much less granules than 200 g of pure starch.
- m. Persorption of particles upon consumption of shredded wheat.
- n. The persorption rate is higher during deep sleep than during day time.
- o. Coffee increases the persorption rate significantly.
- p,q,r. Simultaneous administration of caffeine or prostigmine increases the rate of persorption. Atropine decreases the persorption rate.
- s. Comparison of the persorption rates in young and elderly persons.

DISCUSSION

Particles in the lower nanometer size range can be transcytotically passed through by enterocytes. Larger nanoparticles (up to 3000 nm) can be insorptively taken up by M-cells of the intestinal epithelium (Sass et al., 1990) and removed by macrophages.

But also very much larger, solid particles in the *micrometer* range regularly pass from the alimentary tract into the organism. Virchow's assumption of mechanical causes for the kneading of solid particles into and through the epithelial layer was confirmed. Doubts about a paracellular translocation of microparticles through transitory epithelial leaks have been excluded. Persorption of microparticles is possible where single-layer epithelium covers the mucosa of the alimentary tract, i.e., between the cardia and the anus. Apart from factors of cell disintegration, it is the solid microparticles adjoining the mucosa as an 'abutment' and the mechanical forces of vascular pulsation and motility acting on the particles from every direction that are responsible for the loosening of epithelial cell connections. In the small intestine, there is also the rhythmical change between the compression and suction of the villous "pump". When the intestinal motility is influenced pharmacologically, there is also a change in the persorption rate. What qualitative and quantitative part the constantly hammering vascular pulsation communicated to the mucosa has in the loosening of the epithelial cell connections, in the kneading in and by the epithelial cell layer and in their further transportation has not yet been adequately studied. After the paracellular penetration of the epithelial cell layer, the microparticles can be demonstrated in the subepithelial Grünhagen-Mingazzini area that may be optionally filled with variable quantities of tissue fluid

from which they are rapidly removed. A participation of macrophages in the penetration and removal is not apparent. For the removal of the microparticles from the subepithelial region, use is made of lymph vessel veins; a size selection for the uptake in lymph or blood vessels is already apparent in this phase. The removal via lymph tracts can be traced histologically; it is also shown by the ample evidence of persorbed microparticles in the chyle of the thoracic duct.

An accumulation of persorbed microparticles in mesenteric lymph nodes was not apparent in the pig. In the mesenteric venous blood of dog intestinal segments filled with microparticles, significantly more particles are found than in arterial blood taken at the same time. This shows that some of the persorbed microparticles are removed by veins. Up to now, it has not been possible to make a more exact quantitative and qualitative determination of the proportions removed via the two routes.

The transfer to the peripheral blood stream always takes place as individual particles: microparticles transported via lymph tracts first of all pass through the thoracic duct to reach the pulmonary vascular system where they can embolise small vessels. They can also be seen there in the alveolar lumen after a short time. However, numerous microparticles, even larger ones, pass the pulmonary circulation with the blood stream. Essentially the same process is seen in the liver but the sinusoidal-cholangiolic translocation mechanisms of this copious elimination into the bile and its rapid onset have not yet been satisfactorily clarified in all its phases.

When the determination of the *persorption rate* is attempted, a surprising observation is that the first particles appear in the peripheral blood already

within a few minutes of ingestion and that a first peak value is reached after about 10-12 minutes. The reasons for the multi-peak curve of the number of particles in the venous blood after the peroral – and also rectal – application of microparticles have not yet been adequately clarified. The occurrence of persorption at the same time on the large areas of the alimentary tract and the rapid onset of the elimination from the blood circulation are to be considered here. In addition, there is the removal at varying rates from the mucosa via lymph tracts and mesenteric veins and other factors that quantitatively cannot be precisely determined with this rapid

drift of microparticles into the circulatory blood. There is also the temporary embolisation in smaller blood vessels, distribution, degradation and phagocytosis.

Smaller microparticles, not capable of embolisation, circulate for a longer time in the blood stream than larger particles. Twelve hours after the ingestion of starch suspensions only a few starch-granules can still be demonstrated in the peripheral blood and after 24 hours they have almost completely disappeared. The persorption rate in dogs can be compared more or less with that in man whereas chicken and pigeons display a very much higher rate.

OUTLOOK

The persorption of microparticles is an effect that may be constantly observed in the passage of food through the organism. The embolisation of small vessels by persorbed particles is of interest from the viewpoint of micro-angiology. The long-term deposition of microparticles that are capable of embolisation and consist of potential allergens or contain contaminants is of immunological and toxicological importance. Environmental and industrial

medicine is addressed since industrial and natural dusts passing via the nasopharynx to the alimentary tract are persorbed. A noteworthy observation is the passage via the placenta of persorbed microparticles into the foetal circulation. The phenomenon of the persorption of microparticles still requires numerous supplementary studies; the heuristic value has by no means been exhausted as yet.

LITERATURE

- Donders, F.C.: Untersuchungen über den Übergang fester Moleküle in das Gefäßsystem. *Z. Rat. Med. NF 1*, 415-427 (1851).
- Eberhard, R.F.: Versuche über den Übergang fester Stoffe von Darm und Haut in die Säftemasse des Körpers. *Z. Rat. Med. NF 1*, 406-415 (1851).
- Herbst, G.: Das Lymphgefäßsystem und seine Verrichtung. Vandenhoeck & Ruprecht Göttingen 333-337 (1844).
- Hirsch, R.: Über das Vorkommen von Stärkekörnern im Blut und im Urin. *Z. Exp. Path. Ther.* 3, 390 (1906).
- Hirsch, R.: Über das Übergehen corpusculärer Elemente in den Harn. *Berl. Klin. Wschr.* 45, 331 (1908).
- Marfels, F. and Moleschott, J.: Der Übergang kleiner fester Theilchen in den Milchsaff und das Blut. *Wien. Med. Wschr.* 4, 817 (1854).
- Mensonides, J.A.: De absorptione molecularum solidarum nonnulla. Diss. Utrecht (1848).
- Oesterlen, F.: Über den Eintritt von Kohle und anderen unlöslichen Stoffen vom Darmcanal aus in die Blutmasse. *Z. Rat. Med.* 5, 434-439 (1846).
- Sass, W., Dreyer, H.P., and Seifert, J.: Rapid insorption of small particles in the gut.

- Am. J. Gastroenterol. 85, 255-260 (1990).
- Verzár, F.: Aufsaugung und Ausscheidung von Stärkekörnern. *Biochem. Z.* 34, 68 (1911).
- Virchow, R.: *Arch. Path. Anat.* 4, 538 (1852).
- Virchow, R.: *Verh. Phys. Med. Ges. Würzburg* 4, 350 (1854).
- Volkheimer, G., John, H., Al Abesie, F., and Wachtel, S.: Durchlässigkeit der Colonschleimhaut für korpuskuläre Elemente aus dem Darmlumen und deren Ausscheidung im Harn. *Dt. Ges. Wes.* 16, 1651-1652 (1961).
- Volkheimer, G., Wolf, W., and John, H.: Über die Durchlässigkeit der Darmschleimhaut für oral verabreichte Muskelfasern. *Dt. Ges. Wes.* 17, 413 (1962).
- Volkheimer, G., Schneider, D., John, H., and Wolf, W.: Beobachtungen über einen bemerkenswerten Verschleppungsmechanismus von Ascarideneiern im Wirtsorganismus. *Z. Parasitenkd.* 22, 183-185 (1962).
- Volkheimer, G. and John, H.: Über Kapillarfunktionen in der Lunge. *Z. Ges. Inn. Med. Grenzgeb.* 17, 857-860 (1962).
- Volkheimer, G., Ulbricht, W., Al Abesie, F., John, H., and Wachtel, S.: Beobachtungen zur Resorption korpuskulärer Elemente aus dem Darm und deren Vorkommen im Bereich des ZNS und im Liquor cerebrospinalis. *Psych. Neurol. Med. Psychol.* 14, 129-130 (1962).
- Volkheimer, G. and John, H.: Über die Ausscheidung von Korpuskeln durch die laktierende Mamma in die Milch. *Zbl. Gynaekol.* 85, 561-563 (1963).
- Volkheimer, G.: Durchlässigkeit der Darmschleimhaut für großkorpuskuläre Elemente (Herbst-Effekt). *Z. Gastroent.* 2, 57-64 (1964).
- Volkheimer, G., Hermann, H., Hermanns, E., John, H., Al Abesie, F., and Wachtel, S.: Über die Resorption und Ausscheidung von intakten Hefezellen. *Zbl. Bakt. I Orig.* 192, 121-125 (1964).
- Volkheimer, G.: Mechanism for Elimination of Corpuscular Elements from the Finest Vessels. *Bibl. Anat.* 7, 40-45 (1965).
- Volkheimer, G., John, H., Wiesner, B., Wendlandt, H., Reitzin, P., Dolkeit, K., Aurich, L., Wachtel, S., Reichenberg, C., Parsi, R.A., and Mürdter, G.: Über bemerkenswerte Eliminationsfähigkeiten der glomerulären Gefäße. *Dt. Ges. Wes.* 20, 21-28 (1965).
- Volkheimer, G. and John, H.: Gefäßwandalterationen durch taktile Reize (Intimal Touch Reaction). *Angiologica* 3, 126-139 (1966).
- Volkheimer, G., Schulz, F.H., and Hofer, E.: Über die Altersabhängigkeit der enteralen Persorption von Stärkekörnern. *Z. Altersforsch.* 20, 107-112 (1967).
- Volkheimer, G.: Zerebrale Gefäßverschlüsse durch Nahrungspartikel (Silting-Effekt). *Z. Gerontol.* 1, 360-367 (1968).
- Volkheimer, G.: Das Phänomen der Persorption von Stärkekörnern. *Stärke* 20, 117-126 (1968).
- Volkheimer, G., Schulz, F.H.: Persorption of vegetable food particles. *Qualitas Plantarum et Materiae Vegetabilis* 17, 17-30 (1968).
- Volkheimer, G., Schulz, F.H., Aurich, I., Strauch, S., Beuthin, H., and Wendlandt, H.: Persorption of Particles. *Digestion* 1, 78-80 (1968).
- Volkheimer, G. and Schulz, F.H.: The Phenomenon of Persorption. *Digestion* 1, 213-218 (1968).
- Volkheimer, G., Schulz, F.H., Hofmann, I., Pieser, J., Rack, O., Reichelt, G., Rothenbacher, W., Schmelich, G., Schurig, B., Teicher, G., and Weiss, B.: The effect of drugs on the rate of persorption. *Pharmacology* 1, 8-14 (1968).
- Volkheimer, G., Schulz, F.H., Lehmann, H., Aurich, I., Hübner, M., Hallmayer, A., Münch, H., Oppermann, H., and Strauch, S.: Primary portal transport of persorbed starch granules from the intestinal wall. *Med. Exp.* 18, 103-108 (1968).
- Volkheimer, G., Wendlandt, H., Wagemann, W., Reitzig, P., Schneider, D., Böhm, C., Böhm, M., Eras, B., Gröning, H., Hauptmann, G., Hiller, R., Lorenz, H., Mandelkow, A., and Strauch, S.: Beobachtungen zum Persorptionsmechanismus. *Path. Microbiol.* 31, 51-58 (1968).
- Volkheimer, G.: Persorptionsfähige Partikel in speisefertiger Nahrung. *Ernährungsumschau* 15, 267-271 (1968).
- Volkheimer, G., Schulz, F.H., John, H., Meier zu Eisen, J., and Niederkorn, N.: Persorbed food particles in the blood of newborns. *Gynaecologia* 168, 86-92 (1969).
- Volkheimer, G., Schulz, F.H., Hofer, E., and Schicht, J.: Coffeinwirkung auf die Persorptionsrate. *Nutr. Dieta* 11, 13-22 (1969).
- Volkheimer, G., Schulz, F.H., Lindenau, A., and Beitz, U.: Persorption of metallic iron

- particles. Gut Lond. 10, 32-33 (1969).
- Volkheimer, G.: Persorption. Monograph in the series „Gastroenterologie und Stoffwechsel“ (Eds.: Bartelheimer, Kühn, Becker, and Stelzner). Band 2, Thieme, Stuttgart (1972).
- Volkheimer, G.: Passage of particles through the wall of the gastrointestinal tract. Environm. Health Perspect. 9, 215-225 (1974).
- Volkheimer, G.: Hematogenous dissemination of ingested polyvinyl chloride particles. Ann. NY Acad. Sci. 246, 164-171 (1975).
- Volkheimer, G.: Persorption of particles: Physiology and pharmacology. Adv. Pharmacol. Chemother. 14, 163-187 (1977).
- Volkheimer, G.: Das Phänomen der Persorption (Historie und Fakten). Ber. Phys. Med. Ges. Würzburg NF 85, 239-265 (1977).
- Volkheimer, G.: Persorption of Particles. Mykosen, Suppl. 1, 68-71 (1978).
- Volkheimer, G.: Persorption von Mikropartikeln. Pathologie 14, 247-252 (1993).
- Volkheimer, G.: Das Phänomen der Persorption – Historie und Fakten. Z. Ärztl. Fortbild. 87, 217-221 (1993).