ferment digest other cells or bacteria," etc. That trypsin is the bactericidal agent of the intestinal tract has been shown by Charrin and Levaditi, Zaremba and others, as stated in the first volume. Again, while Weil and Clerc[50] write that "leucocytes do more than englobe bacteria; they submit them to a true process of digestion," M. Labbé[51] says, after referring to the oxidase, fibrin-ferment, etc., found in these cells: "They contain, moreover, a *fibrinolytic* ferment (Leber, Achalme), a casein ferment, a ferment analogous to *trypsin*, a *glycolytic* ferment (Arthus), an *amylolytic* ferment (Rossbach, Zabolotny, Tarchetti), a *lipasic* ferment, which as shown by Poulain plays an important rôle in the assimilation of fats"—briefly all the hydrolytic ferments of the pancreatic juice, and, therefore, the various triads enumerated at the end of the preceding chapter.

The analysis of the question being continued under the next heading, the following are submitted as preliminary conclusions: (1) *that the products of gastro-intestinal digestion, i.e., the peptones, are not, as now taught, absorbed as such by the intestinal mucous membrane;* (2) *that they do not, as now believed, enter the fluid portion of the blood and lymph;* (3) *that they are taken up from the intestinal canal by leucocytes—the digestive leucocytes—which then enter the circulation;* and (4) *that after terminating the digestion of peptones ingested by them, the leucocytes convert the end-products into granulations, i.e., into a compound suitable for assimilation by the cells of the body at large.*

THE GRANULATIONS OF LEUCOCYTES AS THE GRANULES (MICROSOMES) OF TISSUE-CELLS.

The lymphatic system, as is well known, is the intermediary through which the tissues receive their nutrient substances. "In order to nourish the tissues of the body," writes Isaac Ott,[52] "the plasma of the blood is constantly being osmosed through the capillary walls into spaces between the cells of the tissues. Each cell is thus bathed in a plentiful supply of plasma, from which it absorbs what is needed for its nourishment. This escaped blood-plasma, together with some *white cells* which have found their way *into the spaces*, constitute the lymph." Starling[53] also concludes that the only way by which the tissues can obtain their supply of proteid is by this process.

[50] Weil and Clerc: "La leucocytose en clinique," p. 157, 1904.
[51] Labbé: *Loc. cit.*, p. 43.
[52] Isaac Ott: "T. B. of Physiol.," p. 115, 1904.

In the light of the evidence submitted in the first volume and in the foregoing section, the granulations of the leucocytes —the white cells referred to by Ott—are distributed to the tissue-cells. This necessitates their migration through the walls of the blood-capillaries into the lymph-spaces. As is well known, Cohnheim showed that leucocytes did so in the course of inflammatory processes—an established fact. Now, while Starling states that "the tissue spaces, which are filled with lymph, are always found in association with connective tissue," Gulland[54] witnessed, and illustrates in his paper, a leucocyte "fixed in the act of passing through a narrow hole between two bundles of connective tissue and dragging behind it a large number of granulations in a network of fibers." The cell was evidently entering the lymphatics to become one of the many found therein, which include, as stated by Klein,[55] "granular oxyphile, basophile and *amphophile* cells,"—the amphophiles being the neutrophiles which I regard as nutritive leucocytes. The fact that leucocytes can secrete granules in lymph is shown by the behavior of these cells in the alimentary canal. Thus, while Hardy and Wesbrook,[56] we have seen, observed that leucocytes "within the epithelium or the lumen of the gut" showed a marked diminution or complete disappearance of their granulations, Hoppe-Seyler[57] found that the intestinal fluid, apart from its ferments, "was identical with that of the blood-plasma, and of lymph."

Again, there is a distinct relationship between the digestive leucocytosis and the lymph wave accompanying the digestive process. The correspondence between the fluctuations of activity of the digestive process and the amplitude of the lymph wave was recently emphasized by the researches of G. Oliver,[58] which showed among other facts: "that as the digestive wave

[53] Starling: Schäfer's "T. B. of Physiol.," vol. i, p. 311, 1898.
[54] Gulland: Jour. of Physiol., vol. xix, p. 385, 1896.
[55] Klein: "Elements of Histology," 1898.
[56] Hardy and Wesbrook: Jour. of Physiol., vol. xviii, p. 490, 1895.
[57] Hoppe-Seyler: Physiol. Chemie, S. 27, Berlin, 1881.
[58] G. Oliver: Lancet, Oct. 3, 1903.

develops the blood becomes more concentrated; that the ingestion of food produces a rapid flow of lymph into the tissue spaces; that there is complete agreement between the blood-pressure and the exudation of lymph," and finally that "the to-and-fro transfers of fluid from the capillary to the tissue spaces constitute a circulation which appears to suffice for all the requirements of metabolism while the body is in a state of rest." That this coincides with a corresponding increase of leucocytes and their products is shown by the familiar digestive leucocytosis which is especially marked after the ingestion of proteids. Thus, as Hammarsten[59] states, the number of leucocytes may be increased "after a meal rich in *proteid.*"

That the granulations of leucocytes are present in all tissue-cells and that they constitute therein and in cells in general what has been termed their "granules" or "microsomes," is sustained by considerable direct and indirect evidence.

It is now generally recognized that, notwithstanding the complex functions which it fulfills in the body, a protoplasmic cell is but a counterpart of a multitude of similar forms, both vegetal and animal, that lead an independent existence as isolated individuals, viz., unicellular organisms. The amœba is an example of this type, the prototype of our mobile, flowing, leucocytes, as well as of our stationary cells—the muscle-cell, the hepatic cell, the nerve-cell, etc.

"It has long been known," says Verworn,[60] "that roundish granules of different sizes are of wide occurrence within cells, lying in an apparently homogeneous ground substance; they have been termed elementary granules, granula or microsomes." . . . . . . "In many cases only a few such granules are present in the cell; in other cases, the whole cell is thickly filled with them, so that the ground substance between them almost disappears." We are evidently dealing with an important feature of vital functions. E. B. Wilson,[61] for example, places the cell-theory "beside the evolution theory as one of the foundation stones of modern biology," and characterizes the

[59] Hammarsten: "T. B. of Physiol. Chemistry," fourth edition, p. 208, 1904.
[60] Verworn: "General Physiology," p. 63, 1899.
[61] E. B. Wilson: "The Cell in Development and Inheritance," New York, 1897.

granule or microsome as "the most fundamental question of cell-morphology."

Its importance is further shown by the fact that Herbert Spencer attributed to these granules the phenomena of regeneration, development and heredity; that Darwin accorded them an equally prominent rôle in his theory of pangenesis, and that they were likewise regarded as living elements by many other distinguished investigators, including Haeckel, de Vries, Hertwig and Whitman. Indeed, they were the *bio*phores of Weismann, the *bio*plasts of Beale, the *bio*gens of Verworn; they were also the renowned microzymas of Béchamp and Estor which long held sway against Pasteur, and which even now constitute the strongest weapon of the defenders of the theory of spontaneous generation.

The grouping of so many conceptions normally suggests a kinship between them all. Even apparently opposed views assume this relationship, if, in accord with my own view, the leucocytic granulations are considered as nutrient particles which constitute the essential living elements of the cell. This is well shown by the following lines of Herbert Spencer's, quoted from the last edition (1898) of his Principles of Biology: "What these granules or microsomes are—whether, as some have contended, they are the essential *living elements* of the protoplasm, or whether, as is otherwise held, they are *nutritive particles,* is at present undecided."

Even the limited evidence and conclusions I have submitted so far suffice to point strongly to the leucocyte granulations as the "nutritive particles" referred to. We will now see that these granulations and the cellular "granules" correspond in every way.

The nucleus of all cells is composed mainly of two substances, the *chromatin,* thus termed because it is deeply stained by appropriate dyes, and the *nuclear sap,* which takes a lighter tint. "The chemical composition of chromatin is highly complex," says Spencer,[62] "and its complexity, apart from other traits, implies relative instability. This is further implied by the special natures of its components. Various analyses have shown that it consists of an organic acid (which has been called

[62] Spencer: "Principles of Biology," vol. i, p. 259, New York, 1898.

nucleic acid) *rich in phosphorus** combined with an albuminous substance: probably a combination of various proteids. And the evidence, as summarized by Wilson, seems to show that where the proportion of phosphorized acid is high the activity of the substance is great; while, conversely, where the quantity of phosphorus is relatively small, the substance approximates in character to the cytoplasm. Now, (like sulphur, present in the albuminoid base) phosphorus is an element which, besides having several allotropic forms, has a *great affinity for oxygen;* and an organic compound into which it enters, beyond the instability otherwise caused, has a special instability caused by its presence. The tendency to undergo change will therefore be great when the proportion of the phosphorized component is great. Hence the statement that 'the chemical differences between chromatin and cytoplasm, striking and constant as they are, are differences of degree only;' and the conclusion that *the activity of the chromatin is specially associated with the protoplasm.*"

This recalls strikingly the rôle I have ascribed to nucleo-proteid, owing to the large proportion of phosphorus its nuclein contains, and the intense affinity of this element for oxygen. Indeed, it is clear from the above that both *nuclein* and *proteid* are present in the cell, in the identical form in which we found these bodies elsewhere, *i.e.*, as granulations. Now, the granulations of neutrophile leucocytes, which I regard as the nutritive cells, are nucleo-proteid bodies. This was first suggested by Sherrington, then demonstrated by Milroy and Malcolm,[63] whose methods are given in detail in the first volume.[64] Again, Stewart,[65] alluding to the origin of nucleo-proteid, writes: "In shed blood, the *only possible sources* of nucleo-proteid, so far as we know, are the corpuscles and the blood-plates." After dismissing the red corpuscles, he adds: "We have left over the leucocytes and the platelets. The latter are said, and the former *are known* to yield nucleo-proteid when they are broken up in the laboratory."

That leucocytes are capable also of carrying their product

* All italics are my own.—S.
[63] Milroy and Malcolm: Jour. of Physiol., vol. xxiii, No. 3, p. 217, 1898.
[64] *Cf.* vol. i, p. 693, in the first three editions.
[65] Stewart: "Manual of Physiology," fourth edition, p. 41, 1900.

to all parts of the organism is an obvious corollary of their well-known migratory habits, and of the remarkable ease with which they alter their shape in order to pass through minute openings. We have seen that they do so dragging their nucleo-proteid granulations behind them, and that they secrete them. M. Labbé,[66] in common with others, writes: "In respect to foods," the leucocyte "serves, to a degree as yet impossible for us to estimate, for their absorption and transformation, and for their distribution to the cellular elements in need of them." But *what* do they yield to these elements? This question has remained unanswered. As shown above, the only products to which evidence points are their nucleo-proteid granulations.

Another question imposes itself in this connection, however: What is the identity of the plasmatic proteids which, according to the prevailing doctrine, are thought to reach the tissue-cells and to be absorbed by them? The answer is embodied in evidence already submitted, viz., that *there are two kinds of nucleo-proteids*, one for the *tissue-cells*, that alluded to above, and one for the *blood* itself (the fibrinogen to which I have repeatedly referred in the first volume), both secreted by leucocytes. Over thirty years ago Voit[67] showed that the proteid which formed part of the tissue-cells, and which he termed "*organ*-proteid," could not be similar to that present in the blood-stream. The blood proteid he therefore termed the "*circulating* proteid." Liebig, Hoppe-Seyler and Pflüger, in opposition to the additional (and purely theoretical) belief of Voit's that "organ-proteid" had to be dissolved in the plasma and become "circulating" before it could be used in cellular metabolism, showed that "circulating proteid" never underwent *metabolic* changes, and that this rôle was limited to the "organ-proteid." This not only proves that the *plasmatic* proteids are not concerned with tissue metabolism, but it likewise confirms Voit's view as to the presence of two kinds of proteid, *i.e.*, one for the blood-stream and one for the tissues—though both, as interpreted from my standpoint, are products of leucocytes.

Still, the nucleo-proteid destined for the tissue metabolism would be consumed in the oxygen-laden plasma were it not pro-

[66] Labbé: *Loc. cit.*, p. 39.
[67] Voit: Zeit. f. Biol., Bd. x, S. 202, 1874.

tected during its transit from the intestine to the tissues. The leucocytes satisfy precisely this need, by keeping their granulations within their cytoplasm, until in contact with the tissues, where they secrete them. In the first volume, I pointed out that the leucocytes which secreted "fibrinogen" in the blood-stream likewise did so physiologically as required, their secreted granulations combining with the oxidizing substance (adrenoxidase) as needed to sustain, according to the body's needs, the blood's own temperature. Here again, the nucleo-proteid granulations are protected by the cytoplasm of the leucocytes until needed.

Two tests of the question are necessary, however, to place the conclusions herein submitted on a solid basis: (1) the granules or microsomes of the tissue-cells should react to stains as do the granulations of leucocytes; (2) the tissue-cell granules should be shown to act as nutritive particles in keeping with the leucocytic granulations.

Wilson,[68] referring to the two forms of granules found in the chromatic network of cells, says: "They are sharply differentiated by dyes, the *basi*chromatin being colored by the basic anilines (methyl-green, saffranin, etc.) and other true nuclear stains; while the *oxy*chromatin-granules, like many cytoplasmic structures, and like the substance of true nucleoli (pyrenin), are colored by *acid anilines* (rubin, eosin, etc.) and other 'plasma stains.'" Klein,[69] on the other hand, states, referring to "granular leucocytes," that they "behave differently when subjected to staining with aniline dyes. In some the granules stain readily with *acid aniline* dyes—*e.g.*, eosin—so that they become bright red—eosinophile (Ehrlich) or *oxy*phile cells; in others, the granules stain only in *basic* aniline dyes—basophile cells; in still others they stain both with acid and alkaline aniline dyes—neutrophile or *amphophile.*" This applies as well to nerve-cells. Thus, the ganglion-cell "in which," as stated by Ewing,[70] "the chromatic element is in the form of granules irregularly placed through the cell-body," react in the same manner to those reagents. Marinesco[71] found that

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[68] Wilson: *Loc. cit.*, p. 28.
[69] Klein: *Loc cit.*, p. 27, 1898.
[70] Ewing: Arch. of Neur. and Psych., vol. i, No. 3, p. 263, 1898.
[71] Marinesco:. C. r. de la Soc. de biol., Jan. 25, p. 106, 1896.

the "chromophile elements of motor-cells were strongly stained by *basic aniline* reagents," and Benda[72] observed chromatic granules which stained as do the *baso*phile granulations of leucocytes. Held[73] also depicted granules stained by *acid* anilines, and both Colucci[74] and Heimann[75] observed others which, like *amphophilic* granulations, stained with acid and alkaline dyes. It is evident, therefore, that as far as their reaction to stains is concerned, tissue-cell granules and leucocyte granulations correspond.

The second test, *i.e.*, that the granulations nourish the tissue-cells, is no less conclusive. Monti[76] and Lamy,[77] after obstructing the circulation of cerebral vessels by injections of lycopodium, observed a progressive loss of chromatic substance, *i.e.*, of granules, in the dendrites and cell-bodies of the parts deprived of blood. The last-named investigator also observed a gradual loss of chromatic substance in these cells after ligating the aorta. Sarbo[78] noted a gradual disintegration of this substance after ligating the abdominal aorta. Juliusberger[79] obtained a similar effect by compressing this vessel. Ewing[80] verified these results in the human subject, and concluded that "the chromatic structures of these nerve-cells are more immediately affected by changes in their blood supply than by any other influences whose effects upon them have yet been studied." Hodge[81] and Mann[82] observed that "during the repose of the cell, the chromatin accumulates in the nucleus, while during the cell activity this stored-up material gradually disappears."[83] Considered unitedly these facts indicate plainly that it is from the blood and its cells that the nerve-cells receive their chromatic granules, and that their purpose is to nourish these cells.

Chromatolysis, *i.e.*, destruction of the granules, shows, not only that the granules are nutrient bodies, but also that these

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[72] Benda: Neurol. Centralbl., Bd. xiv, S. 759, 1895.
[73] Held: Arch. f. Anat. u. Physiol., S. 396, 1895; S. 204, 1897.
[74] Colucci: Ann. d. Neurol., S. 145, 1896.
[75] Heimann: Virchow's Archiv, Bd. clii, S. 298, 1898.
[76] Monti: Arch. ital. de biol., S. 20, 1895.
[77] Lamy: Arch. de physiol., T. vii, p. 77, 1895; T. ix, p. 184, 1897.
[78] Sarbo: Neurol. Centralbl., Bd. xiv, S. 664, 1895.
[79] Juliusberger: *Ibid.*, Bd. xv, S. 386, 1896.
[80] Ewing: *Loc. cit.*, p. 410.
[81] Hodge: Jour. of Morph., vol. vii, p. 95, 1892.
[82] Mann: Jour. of Anat. and Physiol., vol. xxix, p. 100, 1894.
[83] Bawden: Jour. of Compar. Neurol., May, p. 243, 1900.

bodies are of external origin. "Chromatolysis generally begins at the periphery of the cell and in the dendrons," says Halliburton,[84] "but in advanced cases the whole cell may be affected." That the morbid progression is inward is obvious. The same author says also that chromatolysis alone, however, "is not indicative of cell destruction," and that "the cell may recover its functions later when the abnormal condition passes off." This further indicates that the granules are nutrient elements, *i.e.*, substances of extrinsic origin and bound therefore to penetrate the cell centripetally, their first contact with it being in the intercellular spaces, where granular leucocytes are often met.

On the whole, the identity of (nucleo-proteid) cell-granules as "nutritive particles," using Spencer's expression, is no longer to be doubted. Ewing, after reviewing the labors of several of the above and other investigators, remarks: "Nevertheless the consideration of more recent data leads irresistibly to the conclusion that the chromatic bodies of the nerve-cells represent a state of physiological nutrition." Referring to Nissl's granules, Halliburton[85] also writes: "It can hardly be denied that the substance of which the granules are composed, forming as it does so large a proportion of the cell-contents, and made of a material in which nuclein is an important cônstituent, is intimately related to the *nutritional* condition of the neuron."

The most complicated of all cells, the nerve-cell, has been taken as model because it exemplifies better than any other the function of nucleo-proteid granules, *i.e.*, the chromatic bodies. This rôle is common to all cells; thus Hammarsten,[86] referring to the animal cell in general, writes: "The nucleo-proteids take a very prominent place among the compound proteids of the cell." Indeed, this applies to the entire animal scale, down even to the simplest of living things, the protamœba. Though this unicellular organism contains neither nucleus nor contractile vacuole, the same minute nucleo-proteid granules—chromatin—are clearly visible throughout their entire substance. In fact, the same stainable particles are met with in somewhat less primitive forms, some ciliated infusoria—*Oxy-*

[84] Halliburton: "Biochemistry of Muscle and Nerve," p. 87, 1904.
[85] Halliburton: *Loc. cit.*, p. 87.
[86] Hammarsten: *Loc. cit.*, p. 118.

tricha flava, for example—in which they represent the fragments of broken-up nuclei. In another organism of the same group, *Trachelocerea*, we see the identical stainable granules, but here they are collectively termed a "diffused *nucleus*,"—a nucleus starting from the *periphery* of the cell, where the granules are most numerous, and apparently invading the whole field—the nutrient material penetrating their surface precisely (in the light of my views) as our own cells absorb the nutrient granules supplied to them by leucocytes.

The *Porifera*, a group to which the sponges belong, afford an example of the manner in which the granulations of leucocyte-like cells can subserve nutrition. Thus, Haeckel[87] refers to amœbocytes as "the remarkable amœboid wandering cells, which seem to possess an important physiological function in all sponges." . . . . "Their protoplasm usually encloses," says this distinguished zoölogist, "a variable mass of dark, highly refracting and *intensely staining granules*, and often these enter into the lappet-like processes, or lobopodia of the cell, as in the similar common amœbæ. The amœbocytes of the sponges are *comparable to the leucocytes of the higher Metazoa*." . . . . . . "Their functions are probably multifarious, referring mainly to the nutrition of the sponge. They may be vehicles of food and of reserve nutriments."

The kinship of the amœbocytes with the leucocytes of our own organism becomes striking when the structure of the former is closely examined. Ray Lankester[88] includes among the distinguishing features of the wandering cells of sponges "the quantity of granules with which their cytoplasm is usually packed;" also "the nature of the contained granulations, one kind having coarse, large granules, the other fine granules." He refers to the researches of Fiedler (1888), who describes two kinds of wandering cells, "which he has termed Fresszellen (phagocytes) and Nährzellen (trophocytes) respectively; the former, which occur always near the free surfaces of the sponge body, are concerned more especially with the *ingestion*, and perhaps with the *digestion* of food; the latter, found in all parts, appear to provide for its *distribution*."* We have here a self-

* The italics are my own.—S.
[87] Haeckel: "Rep. of Challenger Exp.," vol. xxxii, 1889.
[88] Ray Lankester: "Treatise on Zoölogy," Pt. ii, 1900.

evident counterpart of the functions of leucocytes in the highest vertebrates, as emphasized in the foregoing pages.

The correspondence between so lowly an animal as the sponge and the highest representatives of the zoölogical scale is not invalidated by the fact that the former lives in the seas while the latter include a vast number that lead a purely terrestrial existence. Forty years ago, Claude Bernard[89] taught that the blood of vertebrates represented "an internal medium in which anatomical elements live as do fishes in water." Indeed, man has not severed his connection with the Oceans in which lived the primitive cells from which he sprang; his blood, we shall see,[90] closely approximates sea-water in composition: he merely carries, therefore, a bit of the Ocean within him. But we must not overlook the difference between a free mobile, unicellular organism, the amœba, for instance, and a cell deprived of migratory motions such as the tissue-cell. The one is able to provide itself with sufficient food, not only because it can reach for it with its pseudopodia, but also because it can, by migrating, increase, when necessary and conditions permitting, its food-supply. The sedentary tissue-cell, imprisoned among its kind, cannot thus satisfy its needs, and Nature meets the want by providing both an amœboid messenger, the leucocyte, and the precise food the tissues need, the granule.

Summarized, this evidence, supplemented by that contained in the preceding section and in the first volume, appears to me to warrant the following conclusions: (1) *that the tissue-cells are not nourished as now taught, by peptones carried to them by the blood-plasma;* (2) *that this function is carried on by leucocytes which migrate through the walls of the capillaries with the blood-plasma, to enter the spaces between the tissue-cells;* (3) *that once in the intercellular spaces the leucocytes secrete their granulations;* (4) *that these granulations are the nutritive materials of the tissue-cells;* (5) *that the granulations penetrate the tissue-cells from the periphery and constitute their granules or microsomes.*

[89] Claude Bernard: Leçons sur les propriétés des tissus vivants," p. 55, Paris, 1866.
[90] *Cf.* this vol., 1367.

THE LEUCOCYTIC FERMENTS AS THE INTRACELLULAR FERMENTS OF TISSUE-CELLS.

Mendel[91] wrote recently (1906): "Enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities of cells in almost every feature of metabolism." Indeed, the tissue-cell does not contain the nucleo-proteid only; it embodies, as shown below, the three agents which carry on the digestive process in the alimentary canal, and which jointly constitute an "enzyme" or "ferment," one of the hydrolytic triads.

The presence of the *zymogen* is shown by that of the ferment of which it is the known precursor. Verworn[92] states that ferments "appear in both animals and plants," and that even in "free cells," *i.e.*, unicellular organisms, "the ferments are of great importance for the nutrition of the cell when these organisms, as is the case with the bacteria, come into contact with organic food and are obliged first to liquefy solid food-stuffs in order to be able to absorb them." That this is carried out by a common ferment was recently suggested by S. H. Vines.[93] "All known proteolytic enzymes of plants are tryptic," says this plant physiologist, "though some of them, such as that of *Drosera*, still await further investigation. This suggestion," he adds, "gains in interest when it is borne in mind that *tryptic* digestion is of general occurrence in the animal kingdom, and is apparently the sole process in many vertebrates. It is not improbable that it may be extended into the proposition that tryptic digestion is a property of all living organisms."

That this applies as well to human and other animal tissues is shown in our own literature: "There is no longer any reason to suppose," says Halliburton,[94] "that the ferment at work is pepsin which had been previously absorbed from the alimentary canal, for Hedin and Rowland[95] have shown that the proteolytic ferment which is present in muscle, as in many other animal tissues (spleen, kidney, etc.), is more like *trypsin* than pepsin in its mode of action." Elsewhere, he reminds the

[91] Mendel: Jour. Amer. Med. Assoc., Mar. 24, 1906.
[92] Verworn: *Loc. cit.*, p. 171.
[93] S. H. Vines: Annals of Botany, vol. xv, p. 572, 1901.
[94] Halliburton: *Loc. cit.*, p. 12.
[95] Hedin and Rowland: Zeit. f. phys. Chemie, Bd. xxxii, S. 341, 531, 1901.