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(Plates XIV. to XVI.)

From the conjoint Laboratories of the Royal Colleges of Physicians (Lond.) and Surgeons (Eng.).

In 1851 Rudolf Virchow[1] described cancer cells containing one or several cavities of various sizes, which were surrounded by hard, almost cartilaginous walls, often possessing a double contour. In certain cases these cavities apparently took the place formerly occupied by the nucleus which had disappeared, whilst in other cases they were not connected with the latter. Some of these cavities divided spontaneously, some contained merely a homogeneous and hyaline mass; in others nuclei and entire cells were found, whilst others again contained nuclear-like bodies and fatty particles. Virchow considered that these cavities and their contents were formed by endogenous division of cells—an opinion which still holds for a large number of these inclusions. The accuracy of these observations was soon confirmed by Wagner;[2] but little attention was paid to the former's discovery until recently, when pathologists, seeking for the cause of cancer, described parasites in the interior of cancer cells. Of late years the number of pathologists who have described intracellular bodies in cancer cells has increased, and it will not be inappropriate to indicate briefly, in chronological order, some of the results obtained by these observers.[3]

Thoma[4] found in the nucleus, and also in the protoplasm of cancer cells, coccidia-like bodies possessing a distinct nucleus, these bodies being easily demonstrated by staining the tissues with hæmatoxylin and eosin.

[1] Rudolf Virchow, "Die endogene Zellenbildung beim Krebs," *Virchow's Archiv*, Bd. i., pp. 107, 130, 483; also Bd. iii., p. 197.

[2] Wagner, "Zur Colloid Metamorphose der Zellen," *Arch. f. physiol. Heilkunde*, 1856.

[3] An excellent summary of these observations by Strœbe will be found in *Centralbl. f. path. Anat. u. allg. Path.*, Bd. ii., pp. 403, 453. 1891.

[4] Thoma, "Ueber eigenartige parasitäre Organismen in den Epithelzellen der Carcinome," *Fortschritte der Medicin*, Bd. vii., No. 11, 1889.

MALASSEZ,[1] who, with ALBARRAN,[2] had ascertained the presence of coccidia in an epitheliomatous tumour of the jaw, demonstrated these organisms to the Société de Biologie on the 23rd of March 1889. In the absence of figures to accompany Malassez's paper, it is difficult to say whether these bodies were really coccidia, but this observer's high reputation as a histologist, and the fact that his observations were corroborated by a zoologist (BALBIANI [3]), make it highly probable that his preparations contained real coccidia.

DARIER [4] shortly afterwards stated that he had seen coccidia in the degenerated epithelium of Paget's disease. The different stages of their evolution corresponded fairly well with the stages of the evolution of coccidia in general. They appeared to be formed by a mass of protoplasm, with or without a nucleus, whilst the task of diagnosing them from epithelial cells was an exceedingly difficult one. The cell surrounded itself with a membrane possessing a double contour, in which numerous small bodies formed through a process of segmentation, the whole structure resembling a cyst containing spores.

WICKHAM [5] confirmed Darier's observations, and illustrated his paper by numerous figures, to which we shall, presently, have to refer. Suffice it to say for the present that Wickham's illustrations hardly bear out the statements he makes, and that we agreee with BORREL [6] in thinking that some, if not all, of the figures described by Wickham do not represent parasites, but depict cells undergoing degeneration, or refer to the endogenous formation of cells. Borrel[7] has, lately, accurately described bodies enclosed in cancer cells, which in our opinion are undoubtedly parasitic, an opinion which this observer is now inclined to share, although in his first paper he denied the presence of parasites in cancer.

In the year following the appearance of Malassez's paper, NILS SJÖBRING [8] described a parasite which occurs in cancer-cells, and traced its life history in the tumour. As far as we can judge from the description given by Sjöbring, and the plates accompanying his paper, some of the structures described by him are undoubtedly parasites (Figs. 12, 14) whilst others are clearly due to invagination or endogenous multiplication of cells.

[1] Malassez, *C. R. de la Société de Biologie*, 23rd March 1889.

[2] Albarran, *C. R. de la Société de Biologie*, 5th April 1889, and *Semaine Médicale*, 1889, No. 15.

[3] Malassez, "Sur les nouvelles psorospermoses chez l'homme," *Arch. de Médecine expérimentale et d'anatomie pathologique*, tome ii., p. 302. 1890.

[4] Darier, *C. R. de la Société de Biologie*, 13th April 1889.

[5] Wickham, "Anatomie pathologique et nature de la maladie de Paget du Mamelon," *Archives de Médecine expérimentale et d'anatomie pathologique*, tome ii., p. 47. 1890.

[6] Borrel, "Sur la signification des figures décrites comme coccidies dans les épithéliomes." *Ibid.*, p. 786.

[7] *Id.*, "Evolution cellulaire et parasitisme dans l'épithélioma." Montpellier, Gustave Firmin et Montane, 1892.

[8] Nils Sjöbring, "Ein parasitärer protozoaartiger Organismus in Carcinomen," *Fortschritte der Medicin*, Bd. iii., No. 14, p. 529, 15th July 1890.

E. SIEGENBEEK VON HEUKELOM[1] found in more than 200 carcinomata, small round bodies, the nature of which he did not determine. Whether these structures were parasites or not it is impossible to say, in the absence of figures to accompany the author's paper.

HAUSER[2] in the same year was unable to satisfy himself of the presence of parasites in the cancerous tumours examined by him.

In December 1890, WILLIAM RUSSELL[3] of Edinburgh claimed to have demonstrated the characteristic micro-organism of cancer, which he designated under the term of fuchsine-body. By means of a special stain he showed that these fuchsine-bodies occurred in little clusters of one up to twenty or more. They formed perfect spheres, and varied in size from 4 μ to 12 μ. They appeared to be perfectly homogeneous and structureless, and the larger clumps were held together by a delicate cementing substance, which stained faintly. He also described the mode of reproduction of these bodies, and classified them under the sprouting fungi (the *sprosspilze* of Nägeli). This paper gave rise to a considerable amount of criticism, and later observers almost universally condemned Russell's views. We need only quote a paper by Shattock and Ballance,[4] who, in consequence of finding similar bodies in sections of senile arteries, in caseating lymphatic glands and in diphtheritic tonsils, concluded that the bodies described by Russell were not micro-organisms. More lately, Klien[5] has arrived at similar conclusions, and suggests the probability of some of these fuchsine-bodies having the same origin as Altmann's cell-granula, which have become larger through assimilation of fat; and, further, that to some extent the two are identical.

From our own investigations we do not feel inclined to reject the whole of Russell's work in the somewhat contemptuous fashion adopted by some writers. To us the truth rather appears to be that, by using Russell's methods, various structures are stained which undoubtedly are not parasites; but it is equally clear to us that Russell's staining method also brings out the characteristic parasites found in cancer. Russell's work certainly reopened the whole question of the parasitism in cancer, and he was the first in England who actually saw and recognised the parasite of cancer. On the other hand, it is to be

[1] E. Siegenbeek von Heukelom, "Ueber intracelluläre Gebilde bei Carcinomen" (Vortrag, gehalten auf dem X. internationalen medicinischen Congress in Berlin, 4–9 August 1890), *Centralblatt für allgemeine Pathologie u. pathologische Anatomie*, Bd. i., No. 22, p. 704, 15th Oct. 1890.

[2] Hauser, "Das Cylinderepithel-Carcinom des Magens u. des Dickdarms," Jena, Gustav Fischer, p. 131. 1890.

[3] Russell, "An Address on a Characteristic Organism of Cancer," *Brit. Med. Journal*, vol. ii., p. 1356, 13th Dec. 1890.

[4] Shattock and Ballance, "A short record of work done on the Pathology of Cancer during the last few years," *Brit. Med. Journal*, vol. i., p. 565. 1890.

[5] Klien, "Ueber die Beziehungen der Russell'schen Fuchsinkörperchen zu den Altmann'schen Zell-granulis," *Beiträge zur path. Anatomie u. al gemeinen Pathologie*, Bd. xi., p. 125. 1891.

regretted that he was unable to obtain a clear differentiation from other structures which have a special affinity for fuchsine.

MAURICE CAZIN,[1] who has given a careful account of the processes of cellular degeneration of cancer-cells, is of opinion that the bodies described by Russell and others are merely cellular degenerations. In another paper[2] the same author gives a careful review of the work on the same subject.

STRŒBE,[3] in his valuable and interesting paper, considers the presence of parasites in cancerous tumours as not proved.

SCHUTZ[4] is of opinion that the bodies described in cancerous tumours as coccidia are simply red corpuscles which have found their way into the cell-protoplasm or nucleus, and there undergo a series of morphological changes. L. PFEIFFER,[5] on the other hand, appears inclined to regard as sporozoa some of the bodies found in cancer cells, and has himself made some interesting observations on the point.

RIBBERT[6] is of opinion that the bodies described as parasites in cancerous tumours, are simply due to a metamorphosis of nuclei; and CORNIL[7] comes practically to the same opinion.

FABRE-DOMERGUE[8] thinks that the coccidia described by Malassez and Albarran are simply degenerated epithelial cells, and has lately repeated this assertion.[9]

BOWLBY[10] and J. HUTCHINSON,[11] jun., described coccidia in Paget's disease of the nipple, but at the discussion which followed their papers, when read before the Medico-Chirurgical Society, THIN[12] of London stated that, in his opinion, these coccidia-like bodies were nothing more than epithelial cells in various stages of degeneration; an opinion with which we entirely agree.

This also appeared to be SHERIDAN DELEPINE'S[13] opinion, for, at the Pathological Society, and at the Congress of Hygiene in August 1891,

[1] Maurice Cazin, "Contributions à l'étude des dégénérescences cellulaires," *Journal de l'anatomie et de la physiologie*, 1890, and *International Congress of Hygiene and Demography*, August 1891.

[2] Maurice Cazin, "La théorie parasitaire du Cancer," *Arch. gén. de Médecine*, Jan. 1892.

[3] Strœbe, "Zur Kenntniss verschiedener cellulärer Vorgänge u. Erscheinungen in Geschwülsten," *Beiträge zur pathol. Anat. u. allgem. Path.*, Bd. xi., No. 1, 1891.

[4] Schutz, "Ueber die Protozoen-und Coccidienartigen Mikro-organismen in Krebszellen," *Münchener Med. Wochenschrift*, 1890, No. 35. See also Strœbe, *loc. cit.*

[5] L. Pfeiffer, "Die Protozoen als Krankheitserreger," Jena, 1890.

[6] Ribbert, "Neue Arbeiten zur Ætiologie des Carcinoms," *Deutsche Med. Wochenschrift*, No. 1, 1891.

[7] Cornil, "Mode de multiplication des noyaux et des cellules dans l'épithéliome," *Journal de l'anatomie et de la physiologie*, 1891, p. 97.

[8] Fabre-Domergue, quoted by Cazin, *loc. cit.*, p. 11.

[9] *Id.*, *C. R. de la Société de Biologie*, April 1892.

[10] Bowlby, "Thirteen Cases of Paget's Disease of the Nipple, with Special Reference to the Causation of the Malady by Psorosperms," *Brit. Med. Journal*, May 1891, p. 1070.

[11] J. Hutchinson, jun., *ibid.*, p. 1071. [12] Thin, *ibid.*

[13] Delépine, "Cultivations of Psorospermiæ," *Brit. Med. Journal*, May 23, 1891, p. 1126; *International Congress of Hygiene and Demography*, 1891, and *Brit. Med. Assoc. Nottingham Meeting*, 1892.

he stated that he had not been able to satisfy himself of the presence of parasites in cancer. At the meeting of the British Medical Association, held at Nottingham (1st August 1892), he repeated his former conclusions.

STEINHAUS,[1] in his first paper, gives two beautiful plates, illustrating various bodies often met with in the interior of cancer cells; some of these bodies, according to this author, may be parasites, but he carefully avoids drawing any conclusions concerning their real nature. In his second paper,[2] he accurately describes various appearances found in epitheliomata which, as he says, cannot possibly be referred to parasitic organisms. In the same number of the *Archiv*, R. VIRCHOW[3] recalls his previous observations on the endogenous formation of cancer-cells, and the appearances described by him in molluscum contagiosum.

WELCH[4] believes that the supposed parasitic bodies of cancer are: (1) masses of keratin, (2) irregular masses of eleidin or keratohyalin, (3) degenerating leucocytes, with or without fragmentation of the nuclei, (4) scattered fragments of nuclei of leucocytes.

E. NOEGGERATH[5] gives a clear account of the various bodies which have been described as parasites, and concludes, from his own investigations, that these bodies are not parasitic in nature. He also states that he has been able to show that all the mysterious bodies found in cancer could be traced to pathological alterations of the nuclei of cancer cells. We must refer the reader for further details to Noeggerath's paper, merely remarking that, in our opinion, the proofs brought forward by this author do not bear out his contention, and that he never appears to have seen the structures described by Soudakewitch and ourselves.

SOUDAKEWITCH'S[6] paper, published on the 25th March 1892, is certainly the most important recent contribution to the literature of cancer. The plates accompanying his paper distinctly show that the bodies he describes are neither due to an endogenous formation of cells, nor to invagination, nor to degeneration of leucocytes, nor to colloid or any other form of degeneration of cancer cells. His observations possess increased importance from the fact that METCHNIKOFF[7] gave it as his decided opinion that the bodies described by Soudakewitch were really parasites.

In the beginning of the year one of us (R.) saw in carcinomatous

[1] Steinhaus, "Ueber Carcinom-Einschlüsse, *Virchow's Archiv*, Bd. cxxvi., p. 533. 1891.

[2] *Id.*, "Weitere Beobachtungen über Carcinom-Einschlüsse," *ibid.*, vol. cxxvii., p. 175. 1892.

[3] "Bemerkung ueber die Carcinomen-Einschlüsse," *ibid.*, p. 188.

[4] Welch, quoted by Noeggerath, *loc. cit.* We regret that we have not been able to find any further reference to the original paper.

[5] E. Noeggerath, "Beiträge zur Struktur u. Entwickelung des Carcinoms," Wiesbaden, J. F. Bergmann, 1892.

[6] Soudakewitch, "Recherches sur le parasitisme intra-cellulaire et intra-nucléaire chez l'homme," *Annales de l'Institut Pasteur*, tome v., No. 3, p. 145. 1892.

[7] Metchnikoff, "Note au sujet du mémoire de M. Soudakewitch," *ibid.*, p. 158.

tumours, bodies which he had every reason to believe were parasitic in nature. In his lecture on cancer, delivered on 7th May 1892, Dr. G. Sims Woodhead[1] referred to our work, and said: "A careful examination of these sections removes all doubt as to the nature of these bodies; they are certainly not the result of degenerative processes. They are not leucocytes or red blood-corpuscles taken into the epithelial cells, though small cells appear to find their way into the proliferating epithelial cells in some cases; equally certain it is that they are not vacuoles. They have, indeed, as Metchnikoff says, all the characteristics of coccidia." On the same day we took the opportunity of demonstrating our preparations to the gentlemen who were present at Dr. Woodhead's lecture.

In June of this year, one of us had the pleasure of showing our preparations to Dr. E. Metchnikoff, director of the Institut Pasteur of Paris. Dr. Metchnikoff not only gave it as his opinion that the bodies to be described presently were parasitic protozoa, but he made the task of publishing easier by drawing several figures for us. We beg him to accept herewith our best thanks for this and many similar acts of kindness.

On 16th July 1892, we published, in the *British Medical Journal*,[2] a short note embodying some of our researches on this subject, and as this preliminary note was being written, Podwyssoszki and Sawtschenko[3] published a paper on the same subject, which we shall have to refer to presently. We will, for the present, merely state that we have little doubt that the bodies described by these authors were probably simply degenerated cancer cells. Since the appearance of this paper Sawtschenko[3] has published a second paper, in which he figures parasites differing entirely from those which he has described with Podwyssoszki.[4]

The material on which our observations are based was taken partly from the operation rooms of the University College, Middlesex, and Cancer Hospitals, and partly from the post-mortem rooms of the same hospitals. Absolute alcohol was chiefly used for hardening, but in some cases the tissues were fixed, in the first instance, by soaking in concentrated sublimate solution. On the whole, however, no advantages appeared to result from the use of sublimate. Small pieces were also fixed by Flemming's solution and by osmic acid, *washed in water for at least* 24 *hours afterwards*, and then hardened in the usual way with alcohol. The sections were always cut

[1] Woodhead, "The Morton Lecture on Cancer and Cancerous Disease," *Brit. Med. Journal*, vol. i., p. 954, May 7, 1892.

[2] Armand Ruffer and Walker, "Preliminary Note on some Parasitic Protozoa found in Cancerous Tumours," *Brit. Med. Journal*, vol. ii., July 16, 1892.

[3] Podwyssoszki and Sawtschenko, "Ueber parasitismus bei Carcinom nebst Beschreibung einiger in den Carcinomgeschwülsten schmarotzenden Protozoen," *Centralblatt für Bakteriologie u. Parasitenkunde*, Bd. xi., Nos. 16 and 17, p. 493, April 16, 1892.

[4] Sawtschenko, "Weitere Untersuchungen über schmarotzende Protozoen in den Krebsgeschwülsten," *Centralblatt für Bakteriologie u. Parasitenkunde*, Bd. xii., No. 1, p. 17, 5th July 1892.

Since this paper was written, Foa ("Ueber die Krebsparasiten," *Centralblatt für Bakteriologie u. Parasitenkunde*, Bd. xii., No. 6, 9th August 1892) has described parasites in cancer, which bear a striking resemblance to those figured by us.

after previous embedding in paraffin, according to the Naples method, and then stained, *secundem artem*.

Biondi's reagent, as prepared by Grübler of Leipsic, proved by far the most valuable stain for cancers hardened in alcohol. One gramme of the powder is dissolved in 80 c.c. of water, and 15 c.c. of a ·5 per cent. solution of acid fuchsine added to it.[1] The sections, after remaining in this solution for 1 hour at least, are washed in water (30 sec.), and passed through 95 per cent. alcohol (1 min.), absolute alcohol (2–5 min.), xylol (2–15 min.), and finally mounted in Canada balsam dissolved in xylol. The only drawback to such preparations is that the colour has a tendency to fade; nevertheless they are exceedingly beautiful (see Plate XIV., Figs. 1–5 and 7–15, also the whole of Plate XV. and Plate XVI., Figs. 30–37) and instructive, even when the particular object in view is not the study of parasites. The nucleus of the cell is green, the nucleolus reddish-brown or red, whilst the protoplasm is orange-red. On the other hand, the nucleus of the parasite is red, and the protoplasm assumes a light Cambridge blue colour. The connective tissue forming the stroma of the tumour is of a brilliant red colour, whilst the small cells infiltrating it show dark green nuclei and red protoplasm. After using Flemming's solution, Biondi's reagent may also be used for staining the protoplasm of the cell, as well as the parasites and their capsule. As a rule, however, the nucleus does not readily take up the green colour, and this must be obviated by previously staining the section in a solution of methyl-green, washing in water, and placing it in a 1 per cent. solution of Ehrlich-Biondi's reagent, prepared in the same way as before, and leaving it in the stain for two hours at least. The section is then mounted in the usual manner.

Solutions of hæmatoxylin or Gerrard's logwood-stain give very fair results, after fixing the tissue with osmic acid or Flemming's solution. The capsule of the parasite is well shown, and the nucleus and rays are also quite distinct, but the drawback to this method is that the contrast between the parasite and the surrounding cells is not marked.

Better preparations are obtained by combining Gerrard's logwood with a solution of eosin, or with a ·5 per cent. solution of rose-bengale in 80 parts of water and 20 parts of absolute alcohol. Nigrosin and saffranin have not proved very satisfactory in our hands.

During the last eight months we have systematically examined every cancer that we have been able to obtain, and so investigated several cases of scirrhus of the breast, of columnar epithelioma affecting the alimentary tract (stomach, intestine, colon, rectum, etc.), cancers of the peritoneum and liver, epitheliomata of tongue and epiglottis, together with the metastatic growths of some of these tumours in the glands and internal organs. In one case, indeed, thanks to the kindness of Sir Joseph Lister, we had an opportunity of examining a recurrent cancer of the breast, in which we were able to demonstrate the presence of the parasite presently to be described.

It was only natural that, when first beginning our investigations, we should fail to find parasites in several instances; but increasing practice enabled us to demonstrate them in almost nearly every cancer we examined. We say almost, advisedly, for since the publication of our

[1] Grübler, in a private letter to one of us, recommends a ·4 per cent. solution of the powder, with the addition of 7 c.c. of a ·5 per cent. solution of acid fuchsine to 100 c.c. of the first solution.

preliminary note we have failed to find them in one case of cancer of the breast, and in two epitheliomata of the tongue, in spite of a very careful search.

And here a note of warning is necessary. It would be a mistake to think that these parasites are found in large numbers throughout the cancerous tumour, and that it is sufficient to cut a few sections of cancer to make sure of finding some. On the contrary, section after section may in some cases be examined and not a single one be found, until suddenly the observer's patience is rewarded by finding a nest of these parasites. Only lately, in the last cancer of the breast we examined, not a single one could we find, until we came close to the edge of the primary tumour, when we were rewarded by finding a considerable number.

In another case of scirrhus of the breast, we did not meet with a single one in the primary tumour, whilst the secondary growths in glands and liver were crowded with them. As we shall see, moreover, the life of such parasites in a cancerous tumour is a precarious one, the cell often surviving its parasites.

Our failure, therefore, to find them in some cases is rather to be attributed to insufficient examination, and we are of opinion that it is a mistake to conclude that because no parasites are seen, therefore no parasites are present in that tumour. It follows also that the next task is to examine systematically the primary growth and secondary tumour of patients dead of cancer, and to note accurately in what part of each the parasites are most frequently to be met with.

In the large majority of cases the parasites of cancer are perfectly spherical. A small nucleus, never absent in well-stained preparations, is surrounded by a comparatively large amount of protoplasm. A distinct capsule is also present, which, although not well-marked in tissues hardened in alcohol, is always plainly visible in carcinomata fixed in Flemming's solution.

The nucleus may be quite round (Plate XIV., Fig. 7; Plate XV., Fig. 18 *g.c.*; Plate XVI., Figs. 20, 21, 23, 25), oval (Plate XIV., Figs. 1, 2,), or somewhat irregular in shape. It generally lies in the centre of the parasite, but not unfrequently it is pushed slightly to one side, though never quite against the side (Plate XIV., Fig. 8; Plate XVI., Figs. 25, 27, 28). Its staining reactions differ from those of the nucleus of the invaded cell, and rather resemble those of the latter's nucleolus. In specimens stained with Biondi's reagent, the nucleus of the parasite, like the nucleolus of the cell, often stains with fuchsine and resists the action of the nuclear dye (Plate XIV., Figs. 1–5). This is not always so, however, for sometimes, especially if the section be somewhat over-stained, the nucleus of the parasite assumes a deep Cambridge blue colour (Plate XIV., Fig. 7). In shape it is often sharply spherical, and is sometimes surrounded by a clear space (Plate XIV., Fig. 5; Plate XV., Fig. 16), whilst in other parasites the nucleus appears to be split up into several small particles (Plate XIV., Fig. 4; Plate XV., Figs. 18–6).

In some cases the clear centre possesses a more highly-stained border, from which very fine delicate rays extend to the periphery (Plate XVI., Fig. 26).

The nucleus may lie perfectly isolated, but, more frequently, fine delicate rays extend from it to the periphery. These rays are best seen in specimens fixed with Flemming's solution, and this at first led us to believe[1] that they were due to the action of the hardening reagent. We have now no doubt that this was an error, as we have found these structures in preparations of carcinomata hardened in many different ways—*e.g.* in alcohol, Müller's fluids, osmic acid, etc., etc.—and after the most varied methods of staining. Their signification, however, is not clear.

The protoplasm of the parasite may be perfectly homogeneous, or it may have a slightly mottled appearance (Plate XIV., Figs. 1 and 2). Occasionally coarser rays are arranged in a concentric fashion at the periphery, but do not reach the nucleus (see Plate XIV., Figs. 10–6). Not unfrequently small granules, presenting the same staining reaction as the nucleus of the parasite, lie scattered through its protoplasm (Plate XIV., Fig. 2), whilst in others we have noticed distinct yellow pigmented bodies, resembling greatly the pigment bodies to which Dr. Woodhead has drawn our attention in the coccidia infesting the rabbit's liver.

The parasite often completely fills the cyst in which it lies, but not always so. Not unfrequently there is a distinct space between it and the cyst wall, and it then appears as if it were floating in the contents of this cyst (Plate XIV., Figs. 1, 2, 5, 7; Plate XV., Fig. 16). This is especially well shown in carcinomata hardened in alcohol.

In preparations fixed with Flemming's solution and stained with aniline dyes, the capsule presents a sharp double contour and retains aniline dyes with great tenacity. We are inclined to believe that this capsule is secreted by the invaded cell and not by the enclosed parasite, as it is continuous with the protoplasm of the cell, and is often quite distinct from the parasite, which sometimes, as we have seen, is perfectly free only in the interior of the cyst.

The parasites above described were found by us in the protoplasm of the cell exclusively. The nucleus never contained them, though not unfrequently, owing to their presence, it assumed a somewhat crescentic shape (Plate XIV., Figs. 1, 2, 4, 13, etc.). Never did we meet with them in the lymph spaces, except in the interior of cancer cells, although occasionally we found specimens in which the parasite seemed almost on the point of leaving or entering the cell (Plate XVI., Fig. 21).

In the majority of cases, an infected cell contains one parasite only, but not unfrequently two, three, or more, and as many as fifteen are found in the same cell. These multiple inclusions may either be enclosed each in its own cyst wall (Plate XIV., Figs. 4–10; Plate XVI., Figs. 21, 23, 27, 29), or several may occupy the same cyst (Plate XV., Figs. 16;

[1] Armand Ruffer and Walker, *loc. cit.*

Plate XVI., Fig. 30). Sometimes indeed several cancer cells fuse together, whilst the walls between the parasitic cysts disappear. In such cases the growth of the parasites increases, and thus they distend the cancer cells more and more, until at last an enormous mass is formed, consisting of four or more huge parasites. Such a condition of things we have tried to illustrate in Plate XV., Fig. 16. The picture, however, gives but a very faint idea of the marvellous appearance presented by such bodies.

We cannot yet give any accurate data as to the frequency with which the parasitic protozoa occur in the primary and in the metastatic tumours respectively, nor in the different parts of the same tumour. In the few cases in which we had the opportunity of examining both the primary and the secondary tumours, the parasites were always more numerous in the latter, and the greatest number were found close to the growing edge. Conversely the more degenerated and the more fibrous the tumour, the smaller was the number of the parasites, and in highly degenerated parts and in the fibrous stroma none at all were met with.

We have already stated that the life of the parasites in the cancer-cells is a precarious one. The parasite evidently does not always thrive in the cell, and nowhere could we demonstrate a reproductive process, unless indeed the presence of the granules of chromatin above noted is to be taken as the first stage of such a process. In many cells, moreover, the parasites take the staining material badly, and their reactions consequently differ from those of the neighbouring parasites (Plate XIV., Fig. 9); whilst in other cells (Plate XIV., Fig. 11) they are plainly undergoing a process of disintegration. In such cases they lose their sharp outlines, and present the appearance of being gradually eaten away. It is not too much to suppose that the cells secrete a substance which destroys the parasite, or at any rate inhibits its growth, just as the giant-cells of tubercle secrete a substance which digests the tubercle bacillus, or causes it to become encapsuled (Metchnikoff).

The cancer cells containing parasites often present perfectly normal appearances, or slight marks of degeneration only. In other cases, however, they become more or less vacuolated (Plate XIV., Figs. 2, 3, 4, 5, 8; Plate XV., Fig. 18 *f.*, etc.), whilst in more advanced stages the nucleus presents characteristic changes. It first loses its property of fixing nuclear dyes, such as methyl-green; its sharp outline then grows dim, and the nucleus fuses more or less with the surrounding protoplasm. In a further stage the nucleus disappears completely, and the whole cell is converted into a kind of cyst, in which the parasite appears to thrive perfectly (Plate XV., Fig. 18 *g.c.*). It is quite within the bounds of possibility that, with the death of the cell, the parasite is finally set free, and finds its way into the surrounding lymph stream.

Thanks to the kindness of Dr. L. Pfeiffer of Weimar, who kindly placed some infected animals at our disposal, we have been enabled to study the same process in the epithelium cells of the kidney of the snail, infected with a parasitic protozoon (*Klossia*). The infected epithelial cell

first increases in size, and then gradually becomes pear-shaped, in which state it is attached to the basement membrane by a thin stalk only, which gradually elongates until the cell becomes detached. The parasite grows, and pressing the nucleus of the epithelial cell against the side, finally causes it to atrophy and disappear. The parasite increases more and more, so that at last the cell is represented merely by a thin shell of protoplasm surrounding the capsule of the parasite. Here, however, the whole cycle of the parasite's life occurs within its host; and the formation of spores, the bursting of the capsule, and the liberation of the young, freely swimming, crescent-shaped bodies are clearly seen. We may again express our thanks to Dr. L. Pfeiffer, who has given us this opportunity of studying this most interesting process.

A few words will suffice to explain the relations of dividing cancer cells to the parasite. We have hardly ever seen a cell holding a parasite in its interior show any signs of division, whereas numerous karyokinetic figures were frequently found in the neighbourhood of infected cells. We are led to conclude, therefore, that if the parasites cause the cells to divide, they act on neighbouring cells, whereas they cause their hosts to perish.[1]

The relation of the leucocytes to the cancer cells and to their contained parasites requires special mention, more especially as the first point is now attracting considerable attention. The fact that leucocytes find their way into cancer cells is by no means new; Klebs[2] and Creighton have both attributed a special rôle to these wandering cells in the etiology of tumours. According to the former author, this phenomenon is chiefly noticeable in young and strongly proliferating growths, and, like all emigration, is dependent on certain disturbances in the circulation. The emigrated leucocytes do not remain for long in the tissue immediately surrounding the blood-vessels, but penetrate into the epithelial layer; and, according to Klebs, it is just in those places where leucocytes are numerous that the largest number of karyokinetic figures and nuclear threads are observed. The leucocytes having penetrated into the cancer cell, undergo a special form of degeneration, so that the non-chromatic nuclear substance of the leucocyte, together with its cell protoplasm, fuses into the protoplasm of the epithelial cell, whilst the chromatic nuclear débris survive. This process Klebs compares to that of intracellular digestion by mesoblastic cells,—noting, however, that the digestion is an incomplete one, as the nuclear substance of the

[1] We can recommend the Ehrlich-Biondi stain to those who wish to study the indirect divisions of cancer cells. They will have no difficulty in recognising the most beautiful, symmetrical and asymmetrical karyokinetic figures, and in convincing themselves of the accuracy of the descriptions given by Hansemann[1] in his two classical papers.

[2] Klebs, "Allgemeine Pathologie," Bd. ii., p. 524.

[1] David Hansemann, "Ueber Pathologische Mitosen," *Virchow's Archiv*, February 1890, and 3rd February 1891, p. 356.

leucocyte resists the process. He believes that the remaining undigested nuclear substance of the leucocyte wanders into the interior of the nucleus of the epithelial cell: "These two constituents of different parentage then fuse together, and the chromatic substance of the nucleus of the leucocyte provides building material for the further development of the nucleus of the epithelial cell. Through this process the latter is, quantitatively, in a better position than before, but, through the absorption of the foreign element, it may also undergo qualitative changes. If we accept the latter hypothesis, we may assume these structures—derived from the chromatic substance of the leucocytes—to be *Keim Körner*;—and they may be considered as the carriers of peculiar properties, brought by them into the dividing epithelial cell. The process would thus nearly resemble the fecundation of the ovum, with this important difference, however, that in the case of cancer this fecundation is effected by a descendant of the mesodermic layer."

Such a theory is bold and original, no doubt; but, unfortunately, the facts observed by others and ourselves not only afford it no support, but are actually opposed to it. In the first place, our investigations have shown us that it is exceedingly rare to find a leucocyte in a dividing cancer cell; so much so, that in several hundred preparations we have very rarely seen a leucocyte in the interior of a cell undergoing division. At the time of writing we have under our eyes sections of a secondary nodule of a cancer of the breast, in which every field shows three or four karyokinetic figures, and not a single leucocyte is to be found in the interior of a dividing cell. We must lay especial stress on the fact that most of the leucocytes contained in cancer cells show no traces of degeneration whatever. On the contrary, their nuclei and protoplasm are perfectly normal, and, as we shall presently see, their functions are in no way impaired. True, Strœbe[1] has described leucocytes undergoing a process of degeneration in the interior of cancer cells; but, without denying the truth of this observer's assertion, our researches show that this process must be of exceedingly rare occurrence. Strœbe, however, like us, has been unable to see the fusion of the chromatic nuclear substance of the leucocyte with the nucleus of the epithelial cell. We agree also with Hauser[2] in thinking that in many cases, *if not in all*, the presence of small isolated chromatic bodies occasionally found in cancer cells, is dependent on an abnormality in the development of the karyokinetic figure, and is certainly not due to the cause suggested by Klebs. After these criticisms there is no need to bring forward the strong arguments which might be brought to bear, from the embryological point of view, against the theory of Klebs and Creighton.

Indeed, Klebs himself, apparently, is not convinced of the correctness

[1] Strœbe, "Celluläre Vorgänge u. Erscheinungen in Geschwülsten," *Beiträge zur pathologischen Anatomie u. zur allgemeinen Pathologie*, Band xi., p. 19. 1891.

[2] Hauser, "Das Cylinderepithel-Carcinom des Magens u. des Dickdarms," p. 73. Jena, 1890.

of his theory, for the lines following the passage quoted above run as follows:—"Perhaps it is for the present more correct to consider this process as an importation of raw material possessing no biological properties." We give this passage at length, because the idea is reproduced in some form or other in the papers of the two other observers just referred to. Hauser[1] states that if the migration of leucocytes into cancer cells is of any importance, it can only be because the leucocytes undergo a process of degeneration in the interior of the cells, and are digested and so used up as food material. Strœbe comes to a similar conclusion, but he adds that he has often seen many leucocytes wander into degenerated cancerous epithelial cells, and that, in the latter case, the penetration of leucocytes into the cell has the signification of a reaction against the tumour cells, which may then be considered as foreign bodies. We must observe, however, that in degenerated parts of the tumour it is rare to find leucocytes wandering into degenerated cells; the leucocytes appear to have the same contempt for dead cancer cells that they have for dead micro-organisms.

Our observations do not bear out the theory that leucocytes serve as food for cancer cells. On the contrary, we are of opinion that mesoblastic cells enter the cancer cells in order to fulfil there the functions which they fulfil in every part of the body of every animal, namely, that of destroying and getting rid of any foreign bodies which have entered the organism. In other words, the leucocytes enter the cancer cells and destroy the parasitic protozoon, just as they wander to the point of inoculation in order to destroy the bacillus Chauvœi when this micro-organism is inoculated into a rabbit.

In our experience, not only did we find no traces of degeneration in the leucocytes which had penetrated into cancer cells, but, near the growing edge of cancers, as well as in other parts, we often found numerous perfectly healthy leucocytes in the interior of cancer cells; and, in most cases, the cells containing leucocytes were those which were infected by the parasites previously described. The leucocyte not unfrequently wanders into the very centre of the protozoon (Plate XIV., Fig. 12), and, as a consequence of this penetration, the parasite degenerates not only in its centre (Plate XIV., Fig. 13; Plate XV., Fig. 18 *a*), but also at the periphery. The parasite becomes granular, loses its regular outline, takes up the staining fluid irregularly, and presents evident traces of degeneration. In other cells the leucocyte surrounds the parasite altogether, and the latter (Plate XIV., Fig. 13) then becomes granular and slowly disintegrates. In a more advanced stage the parasite is completely replaced by one or more leucocytes (Plate XIV., Figs. 14, 15; also Plate XV., Fig. 18 *a.c.*), as the former has been completely eaten up by the invading mesodermic cell.

We have hitherto seen the leucocytes play a part in the destruction of the cancer parasite, but something may fitly be added about another

[1] Hauser, *loc. cit.*, p. 73.

extremely interesting process occurring in cancerous tumours, namely, the destruction of cancer cells, by the connective tissue forming in the cancerous tumour. At the edge of a growing carcinoma of the liver, for instance, the cancer cells are in some places seen in close contact with the liver-cells; in other places, however, the edge is infiltrated by a large number of small round cells, which are either emigrated white corpuscles or, as Heidemann[1] believes, are derived from resting connective tissue elements. We must plainly state, however, that our observations do not confirm the latter theory. However this may be, there is no doubt that from those places where the small cells accumulate, new delicate connective tissue grows into the spaces left between the advancing cancer cells. As we approach the older parts of the tumour, this connective tissue, which stains red with fuchsine, grows in quantity, and is gathered together into thick strands, forming the real stroma of the tumour, and subdividing the tumour into alveoli. Sending out thin offshoots, the hard connective tissue insinuates itself between the cells of the alveoli (Plate XV., Figs. 2, 3), and sometimes, indeed, a thin strand will force itself into an epithelial cell. As this stroma increases in amount, the cancer cells diminish, and not unfrequently a cancer cell, sometimes with a parasite in its interior, is absolutely imprisoned by strands of this connective tissue. The cancer cells do not atrophy simply, as is generally supposed, through the pressure exerted on them by the growing connective tissue, but, on the contrary, the process through which the cells are destroyed is a true digestive action exerted by the connective tissue on the cancer cell, and in some cases probably also on the enclosed parasite.

The cancer cell enclosed in the connective tissue at first swells up distinctly (Plate XV., Fig. 17 *a*, and Fig. 18 *f*), and though the connective tissue may be apparently in close contact with it the cell itself may be two or three times its original size. At the same time the protoplasm becomes vacuolated and assumes a dirty brownish colour, while the nucleus is of a greenish-black colour, and loses its well-defined margin. In a further stage the protoplasm is gradually eaten away, whilst, not unfrequently, a distinct vacuole, staining orange, forms round the degenerated cell. The protoplasm finally disappears, but débris of the nucleus are found when the remainder of the cell has already vanished. At the periphery of the whole tumour one not unfrequently finds places where the growth of the tumour has been completely arrested by its encapsulation in connective tissue.

It is interesting to compare cancer in that respect with a class of tumours also caused by protozoa, namely, the coccidial tumours of the rabbit's liver. We need not describe here the peculiar glandular-looking tumours surrounded by their capsule of connective tissue, nor the typical parasites, naked or encysted, lying inside the cells or in the

[1] Heidemann, "Ueber Entstehung und Betheiligung der Kleinzelligen Infiltration bei Carcinomen," *Virchow's Archiv*, Band cxxix., p. 77, July 1892.

lumen of the tubes. We need only refer our readers to the admirable descriptions of Malassez,[1] L. Pfeiffer and R. Pfeiffer,[2] and come at once to the point which interests us more specially.

If we examine the liver of a rabbit which has survived the more acute form of the disease, and in which this has become chronic, we find here and there a tumour in which the connective tissue forming the capsule of the tumour has been broken through by a mass of small round cells. These cells then penetrate between epithelium cells and coccidia, force their way even into such of the latter as have surrounded themselves with capsules and eat up extra- and intracellular parasites alike. In a later stage a dense connective tissue forms and remains as the only trace of what was once a coccidial tumour, but at the periphery of this connective tissue, true giant cells, filled with more or less degenerated coccidia, are found for a long time after the disease has been apparently cured.

We see, therefore, both in the coccidial disease of the rabbit and in cancer, the wonderful part played by the cells derived from the mesoblastic layer in defending the organism against attacking parasites. The law, which Metchnikoff has established, holds good not only for vegetable but also for animal parasites, and the struggle for life is as marked and as easily followed in cancer or the coccidial disease of rabbits as in any infectious disease caused by vegetable micro-organisms.

We have not attempted to classify the parasites we have described, because in our opinion it is useless to do so before the whole of the parasites' life history is known to us.

A few words may now fitly be devoted to the consideration of other structures met with in cancerous tumours, and which, in some cases at least, have been mistaken for parasites.

The first point to consider is whether the parasites just described can by any chance be mistaken for cells which have multiplied endogenously, or for cancer cells invaginated into each other when the knife has passed through the invaginated portions. If any one will place a cigarette in a cigarette-holder and cut a section at the mouth of the holder, the cigarette in the section would appear as if wholly contained in the holder, whereas, as a matter of fact, it would only be partly so. Similarly in cancer, cells often get partly invaginated into each other, and, in sections, they appear as if one was completely enclosed within the other, whereas only a small part of the one is contained within the other. Accurate descriptions of such cells have lately been given by Steinhaus[3] and Borrel,[4] and there can be no doubt that some of the

[1] Malassez, "Notes sur la psorospermose du foie chez le lapin domestique," *Archives de médecine expérimentale et d'anatomie pathologique*, tome iii. p. 1. 1891.

[2] R. Pfeiffer, "Beiträge zur Protozoen Forschung. Die Coccidien Krankheit des Kaninchen." Berlin, Augustus Hirschwald, 1892. See also L. Pfeiffer, "Die Protozoen als Krankheitserreger." Jena, 1891.

[3] Steinhaus, *loc. cit.*

[4] Borrel, *loc. cit.*

figures described as coccidia by Sjöbring, Wickham, and Delépine were really invaginated cancer cells. Moreover, such cells undoubtedly degenerate, and then assume a deep dirty colour, whilst the chromatin is transformed into a homogeneous mass lying in the centre (Plate XVI., Figs. 35, 36, 37).

If we examine carefully a few sections which contain parasites and invaginated cells, and cells which have multiplied through endogenous division, we shall have no difficulty in drawing a distinction between them. In the first place, through no process of endogenous formation whatever, and through no process of invagination, can we explain the presence of 4, 7, or more such bodies, as are represented for instance on Plate XIV., Fig. 4.

One not unfrequently sees well-defined parasites either in the external[1] or in the enclosed cell. Both cells and the enclosed parasites are, in such cases, perfectly distinct from each other. It is only in cases of degenerating cells that a confusion might arise, but, in such a case, the perfectly definite structure of the parasite will at once solve any doubt. No one could possibly mistake any of the figures drawn on Plate XIV. or Plate XVI. (Figs. 19–29) for the intracellular inclusions drawn in Plate XVI. (Figs. 35–37), or for those figured by Borrel and Steinhaus in their valuable papers.

It is far more difficult to distinguish the parasites we have described from various bodies often found in cancer cells, which appear to us to be of a degenerative nature. Such a body has been represented in Plate XVI., Fig. 31 *a;* it closely resembles some of these figures, and those described as parasites by Podwyssoszki and Sawtschenko.[2] They consist of small rounded masses of protoplasm, part of which may stain with a nuclear dye (methyl-green), whilst the other part stains with fuchsine. Several may occur in one cell, and they are most frequently found near the *degenerated parts of the tumour*, an observation also made by Podwyssoszki and Sawtschenko. In some cases indeed the whole cancer cell is converted into one of these masses. We are of opinion, therefore, that these bodies are of a purely degenerative nature, and the fact that we have, in some cancers, found large degenerated tracts, consisting almost entirely of such bodies, and in which their origin from cancer cells could be followed, is in favour of our contention.

In order to see whether colloid and other degenerated cancer cells could in any way simulate the parasite above described, several colloid cancers as well as degenerated parts of other cancers were carefully examined with all the dyes used by us to demonstrate the presence of parasites. Nowhere did we find the slightest resemblance between the degenerated cancer cells and the parasites we have described, and after what we have said in the text, we think it unnecessary to point out

[1] Borrel, *loc. cit.* In Plate II., Fig. 2, he has figured such a cell, in which the outer cell, the division of the inner cell and eight parasites are clearly seen.

[2] Podwyssoszki and Sawtschenko, *loc. cit.*, Plates I. and II.

the differences between leucocytes or red blood-corpuscles and the intracellular protozoa.

A few words, however, must be added concerning an appearance often found in the nucleus of the cancer cell. In some cases of cancer the nucleolus stains deeply with fuchsine (Plate XVI., Figs. 32, 33 *a*, 34), whilst in others a kind of clear space forms round the nucleolus so that it appears to be contained in a kind of cyst. Not unfrequently it breaks up into several small particles, which lie in a clear space in the centre of the nucleus. At one time we were doubtful whether these appearances might not represent the first stages in the development of the parasite, but we soon gave up this idea, as these various appearances could all be traced to the original nucleolus, and were present sometimes in non-cancerous cells also. Some of these nucleoli resemble the structures described by Russell as fuchsine bodies, and were, no doubt, mistaken by this author for parasites.

In a future paper, one of us hopes to give an account of the localisation of the cancer parasites in various kinds of cancer, so as to enable other observers to find them without so much labour as is at present necessary.

There only remains for us to thank the Committee of the Laboratories for the facilities afforded us in carrying on the inquiry.

EXPLANATION OF PLATES.

PLATE XIV.

Figs. 1, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, were drawn by Dr. E. Metchnikoff.

Fig. 1.—Cancer of Stomach. Secondary nodule in liver—Nucleus of cancer cell stained green. Nucleolus red. Nucleus of parasite red. Alcohol hardening. Ehrlich-Biondi staining. Zeiss Oc. 3 Obj. $\frac{1}{18}$ (1200 diameters).

Fig. 2.—From the same cancer. Notice the chromatic corpuscles in parasite. Zeiss *id.*

Fig. 3.—From the same cancer. Notice vacuoles in protoplasm of cell. The nucleus of the parasite is very small. Zeiss *id.*

Fig. 4.—From the same cancer. This cell contains four parasites. Zeiss *id.*

Fig. 5.—From the same cancer. Large parasite with large red nucleus. Zeiss *id.*

Fig. 6.—From a scirrhus of the breast. Nucleus of cell yellow, due to insufficient staining with methyl-green. Nucleus of parasite red. Faint rays extending to periphery. Capsule with double contour well marked. Hardening in Flemming's solution and alcohol. Ehrlich-Biondi stain and methyl-green. Oc. 3 Obj. $\frac{1}{12}$th.

Fig. 7.—From a cancer of stomach. (The section was somewhat too deeply stained.) Nucleus of parasite blue. Well-marked rays extending to periphery. Well-marked degeneration of cancer cell, the nucleus of which has disappeared. Alcohol hardening. Ehrlich-Biondi staining. Beck Oc. 3 Obj. $\frac{1}{12}$th.

Fig. 8.—From the same cancer as Figs. 1-5. The cancer cell is greatly vacuolated, and contains one parasite. Beck *id.*

Fig. 9.—From the same cancer. The parasite no longer retains the blue colour. Zeiss *id.*

Fig. 10.—From a scirrhus of the breast. Two parasites contained in one cancer cell. Alcohol hardening. Ehrlich-Biondi staining. Zeiss *id.*

Fig. 11.—From the same cancer as Figs. 1-5, 8, 9. Cancer cell containing degenerated parasite. Zeiss *id.*

Fig. 12.—From the same cancer. The cancer cell contains a parasite and a multinucleated leucocyte which has wandered to the centre of the parasite. Zeiss *id.*

Fig. 13.—From the same cancer. A multinucleated leucocyte has surrounded a parasite. Zeiss *id.*

Fig. 14.—From the same cancer. The parasite has been replaced by a leucocyte. Zeiss *id.*

Fig. 15.—From the same cancer. The parasite has been completely destroyed by four multinucleated leucocytes. Zeiss *id.*

Plate XV.

Fig. 16.—Two cancer cells joined together and distended by four huge parasites—*a*, *b*, *c*, *d*. Nuclei of parasites. Vérick Oc. 3 Obj. $\frac{1}{18}$th.

Fig. 17.—Section through the fibrous stroma of a cancer of the liver.

a. Cancer cell hypertrophied and beginning to be digested. *d*. Partly digested cancer cells—the nuclei only remaining. *e*. Partly digested cancer cell. Beck Oc. 1 Obj. $\frac{1}{12}$th.

Fig. 18.—Sections through an alveolus of a secondary nodule in the liver of a carcinoma ventriculi. The fibrous tissue is red, and is beginning to invade the alveolus.

a. A cancer cell in which the parasite has been destroyed by a leucocyte.
b. Parasite inside the cancer cell. *n*. The degenerated nucleus of the cancer cell. *c*. Leucocyte entering cancer cell.
d. Parasite inside cancer cell. The nucleus is not well marked.
e.g. Cancer cells converted into cysts containing each a parasite with a well-marked red nucleus.
f. Cancer cell undergoing degeneration and showing a huge vacuole. Beck Oc. 1 Obj. $\frac{1}{12}$th.

Plate XVI.

Figs. 19-29.—From a cancer of the breast, fixed in Flemming's solution, stained with methyl-green and Biondi's reagent. Beck Oc. 1 Obj. $\frac{1}{12}$th.

Fig. 30.—Two parasites in a cancer cell. From a photograph by Dr. Woodhead.

Fig. 31.—A nest of cancer cells containing a pseudo-parasite. For particulars see Text. Beck Oc. 3 Obj. $\frac{1}{12}$th.

Fig. 32.—Cancer cell from a case of carcinoma ventriculi. A nucleolus surrounded by a clear cyst-like space. Beck *id.*

Fig. 33.—Represents another similar condition.

Fig. 34.—Represents the fragmentation of the nucleolus.

Fig. 35.—From a case of epithelioma of the tongue. An invaginated cell simulating a parasite. Beck Oc. 1 Obj. $\frac{1}{12}$th.

Figs. 36 and 37.—*Id.* The invaginated cells are beginning to degenerate. Beck *id.*

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 9.

Fig. 10.

Fig. 11.

Fig. 12.

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 16.

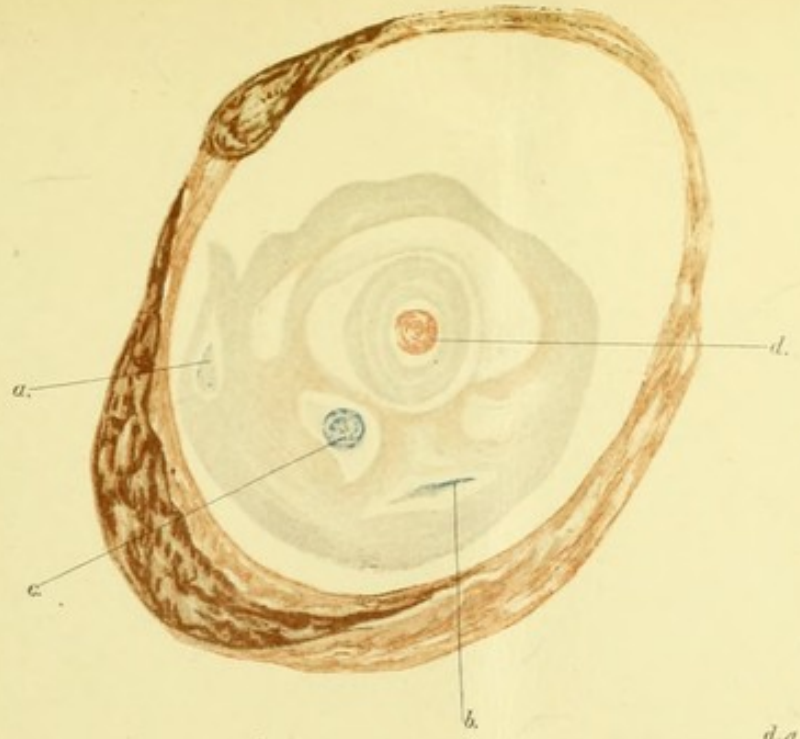

Fig. 17.

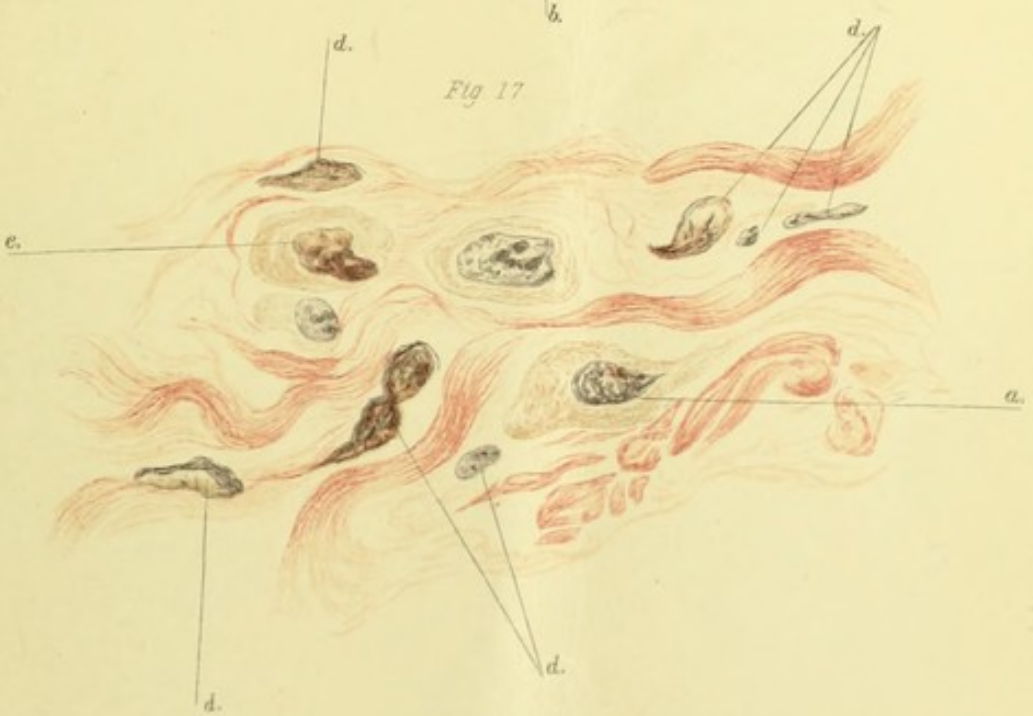

Fig. 18.

Fig. 19.

Fig. 20.

Fig. 21.

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Fig. 28.

Fig. 29.

Fig. 31.

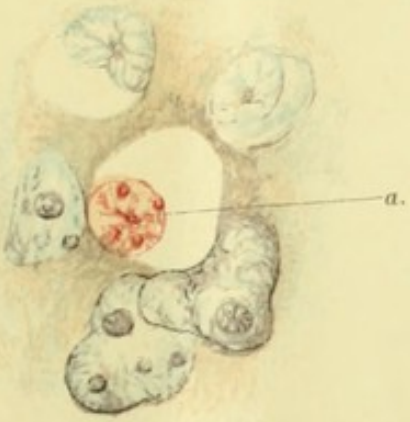

Fig. 30.

Fig. 32.

Fig. 33.

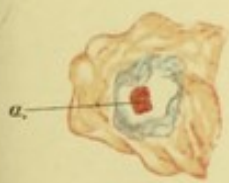

Fig. 34.

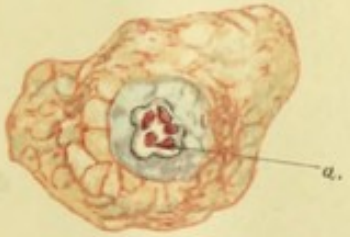

Fig. 35.

Fig. 36.

Fig. 37.