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RETINAL HÆMORRHAGES AND MELANÆMIA AS SYMPTOMS OF AGUE

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RETINAL HÆMORRHAGES AND MELANÆMIA AS SYMPTOMS OF AGUE.*

F. V., AGED twenty, of mixed Scottish and Hindoo blood, was admitted into the London Hospital on November 17, 1876. He stated that six years previously, when in India (his native country), he had had an attack of dengue during an epidemic of that disease. For about a year prior to admission he had been making voyages between Calcutta and the Cape as an ordinary seaman, but during this period his health was good.

On November 3 he reached London, having had during the voyage from Calcutta, on one occasion only, a fit of ague—that is to say, he shivered and felt cold and then felt very hot. There was no repetition of the attack whilst he was at sea. The day after he reached this country, however, he had a severe paroxysm, which was repeated every day until he came under observation. On the evening of admission his temperature was taken hourly, and was found to rise rapidly from 98° to 107° Fahr. He had the usual rigor, hot stage, and sweating stage of his disease. His spleen was found to be considerably enlarged. There were no abnormal physical signs in his chest, excepting a few râles. The main interest of his case lay in the fact that Mr. Atkinson, the House-Physician, found recent hæmorrhages in each retina on the night of admission. These presented the streaky appearance so often assumed by hæmorrhages in this situation, and were chiefly seen along the course of the larger vessels, especially arteries, which they in places obscured. Sprinkled about the fundus, and most numerous near the disc, were many small round bright spots, resembling pinholes pricked in a piece of paper held up against the light. The retinal vessels were of normal size, and their sheaths did not appear thickened. These hæmorrhages were carefully observed day by day, and were seen to fade away gradually; and as each died away it left to mark its former situation one of the shiny white spots of which mention has been made above. It may be here stated

* Read before the Hunterian Society, March 28, 1877.

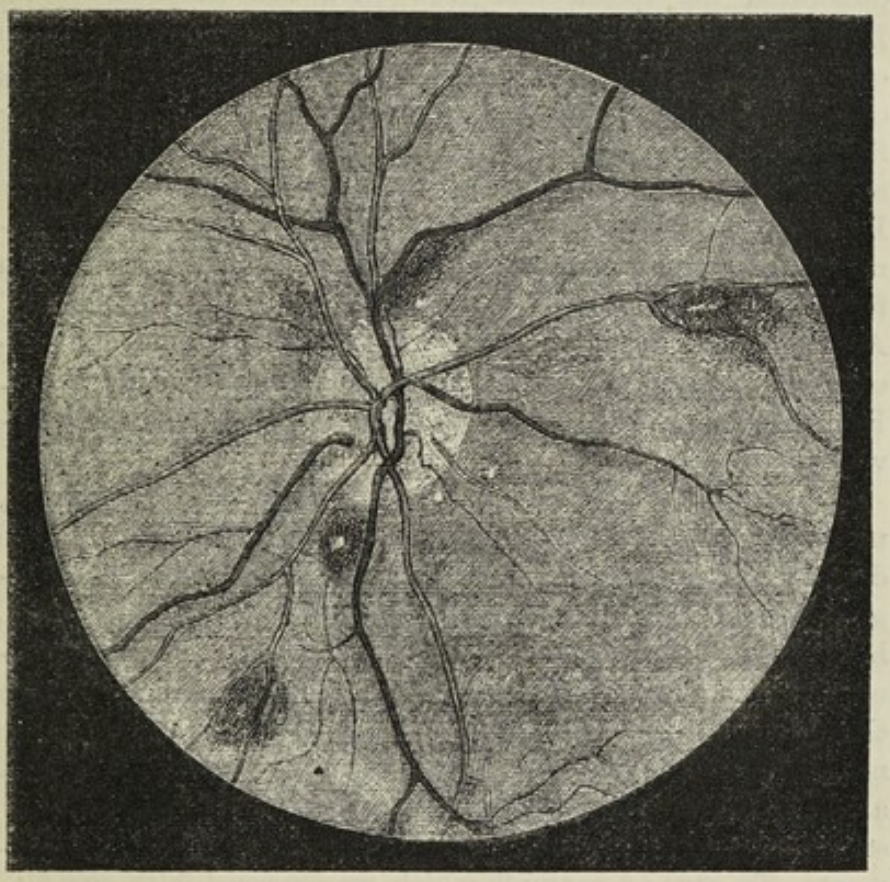
that the patient had neither albuminous urine nor other symptoms of Bright's disease.

His blood was examined under the microscope, and found to contain pigment. When a drop was taken from the pricked finger the following appearances were observed with a Hartnack's objective No. 7, ocular No. 3:—Coloured (red) corpuscles of natural size and appearance; a few large corpuscles of the same tint as the red blood-corpuscles, but twice or three times as large, destitute of any nucleus (macrocythæmia); colourless (white) corpuscles free from pigment; colourless corpuscles containing pigment granules. The pigment granules of brownish-black colour (malaria-melanin) when in small quantity were mostly arranged concentrically around the nuclei; when more abundant they completely obscured the latter. Sometimes the pigment had a stellate arrangement; at other times it completely occupied the corpuscles, which then appeared as brown or black spherical bodies. The nature of the corpuscles containing the pigment was shown by the amœboid movements which took place. There were some large protoplasmic flakes, three times the size of an ordinary colourless blood-corpuscle, also containing pigment granules. Free pigment was not regarded, as it might have had an extraneous origin. The blood was examined on several occasions, and on each the pigmented cells dotted the field of the microscope, and could not have escaped detection. They were abundant on the day that Mr. Walker made a sketch of the appearance of the blood. Wishing to have a drawing of the pigment cells on a larger scale than that adopted by Mr. Walker, special arrangements were made one morning for the purpose, but, when the finger was pricked and blood placed under the microscope, scarcely a pigment cell could be found—indeed, only three or four examples from amongst many slides. This occasion was a few days before the patient's discharge. His blood was examined once or more between then and his leaving, but there was no reappearance of the melanæmia in the degree observed when the first examinations were made.

A few days after admission, having ascertained that we had to deal with a quotidian ague, and having found out at what time a rise in his temperature might be expected, thirty grains of sulphate of zinc were administered shortly before the expected paroxysm. This, as was desired, caused a copious emesis; but it did not altogether prevent, though it modified, the expected rigor. It was followed up by three-grain doses of sulphate of quinine, and no further exacerbation occurred. The patient rapidly improved, and soon recovered from the state of prostration to which the ague had reduced him.

The retinal hæmorrhages first seen gradually faded away until, on December 10, there were no traces of them, except the shining dots, which remained unaltered when he was discharged. On December 20, however, on examining the patient's fundus, I discovered a new hæmorrhage of an entirely different character from those previously seen. It was round in shape, with a sharply defined margin, and was of a uniform dark red colour. It was not at all streaky, like the others previously observed. It gradually altered in colour, the centre becoming first purple and then yellow, and much

Fig. 1.



(From a drawing by Mr. Basil Walker soon after admission.)

paler than the circumferential portion, whilst the latter became, as it were, frayed out. In this condition it was when the patient left the hospital, and returned in good health to his seafaring life.

There are two features of special interest in the case I have read: these are the hæmorrhages into the retinæ and the melanæmia.

1. Retinal hæmorrhages (or hæmorrhagic retinitis, as the condition would be described by many ophthalmic writers), so far as I am aware, have not been noticed specially in connexion with ague. In fact, the observations recorded of the condition

of the retinæ in malarial disorders are few in number. Dr. Hammond, in a paper published in the *Transactions of the American Neurological Society* in 1875,* on "Pigmentary Deposits in the Brain resulting from Malarial Poisoning," has described ophthalmoscopical alterations from melanæmia, the result of malarial poisoning. In one case Dr. Hammond says, "Upon examining the fundus of the eye with the ophthalmoscope I found double optic neuritis, worse on the left side than on the right, and large deposits of pigment in both retinæ, especially the left. These masses were stellate in form, and followed, mainly, the course of the arterial branches. I then punctured the spleen and drew off a few drops of blood. Examined by the microscope it was found to contain a large quantity of free pigment as well as numerous pigment-holding cells." Professor Roosa examined this patient, and confirmed Dr. Hammond's observations as to the ophthalmoscopic appearances. Of another case of malaria with choreic symptoms Dr. Hammond says, "On examining the eyes with the ophthalmoscope, I found numerous deposits of pigment, stellate in form, along the course of the arterial branches on both sides." And of another case he says, "There were no abnormal ophthalmoscopic appearances beyond choked disc on both sides." Dr. Hammond does not appear to have observed retinal extravasations in his cases.

[Since reading this paper I find that M. X. Galezowski, under the head of "Affections de la Rétine et du Nerf Optique dans la Fièvre Palustre," at page 190 of his "Traité Iconographique d'Ophthalmoscopie" (Paris, Baillière et Fils, 1876), has described the occurrence of retinal extravasations in connexion with ague. He writes—"The accidents which occur in the different forms are proportionate to the gravity of the malarial diathesis. In the common form we have distinguished a kind of apoplectic and exudative retinitis, with peripapillary serous infiltration, which yields readily to antiperiodic treatment. To give an example which we observed with our distinguished friend and colleague Dr. Noel Guéneau de Mussy. A schoolboy was seized with violent headache and intense fever; some days later he complained of defective sight, and on examining him with the ophthalmoscope we found double neuro-retinitis with multiple hæmorrhages. After an emetic the disease presented all the characters of a tertian ague, and later fifty-centigramme doses of sulphate of quinine administered for some days produced a cure both of the fever and of the neuro-retinitis." M. Galezowski also mentions atrophy of the papilla and marked diminution of the central vessels in cases of chronic malarial poisoning.]

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* Republished in his "Diseases of the Nervous System."

But whilst hæmorrhages into the retina do not appear to have attracted attention in connexion with malaria, hæmorrhages into the brain and its membranes have been described by most writers on the anatomy of the disease. Frerichs * states that obstruction of the capillaries by pigment and fibrinous-like coagula leads to the formation of numerous capillary apoplexies. He states that Planer described eight cases in which small extravasations were scattered through the grey and white substance of the brain. He adds, "These numerous hæmorrhages have not come under my own observation, but in two cases I have observed extravasations into the meninges." Further on he writes, "I have seen paralysis make its appearance suddenly, and here capillary hæmorrhage was found." Niemeyer says, † "In *autopsies* of persons who have died of pernicious intermittents we often find signs of melanæmia, and occasionally remains of inflammative effusions of blood, or excessive hyperæmia in different organs. Hertz, in his exhaustive monograph on "Malarial Diseases," ‡ mentions "numerous punctiform extravasations which have been thought to depend on blocking up of the capillaries by means of pigment, but which Heschl says may exist independent of the formation of pigment matter, and represent capillary aneurisms." Wagner § also mentions that capillary hæmorrhages have been found in the brain in connexion with malarial melanæmia, and also in cases of malarial poisoning without melanæmia.

It would, therefore, appear that hæmorrhages into nervous structures are not unfrequently met with in fatal cases of malarial diseases. The hæmorrhages are not confined to these parts, however. Hertz ‖ states that ecchymoses are found in the endocardium and pericardium, and small hæmorrhages have been found in the heart-muscle. The liver is sometimes found studded with apoplectic spots, and the mucous membrane of the stomach and intestines has been found ecchymotic.

But besides these post-mortem appearances, hæmorrhages are not at all uncommon during life and in non-fatal cases. Intermittent hematuria is a well-known malarial affection. Hertz writes—"Hæmorrhages from the nose are frequent"

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* "Clinical Treatise on Diseases of the Liver" (New Sydenham Society translation), vol. i., page 327.

† "Text-book of Practical Medicine" (American translation), vol. ii., page 623.

‡ "Ziemssen's Cyclopædia of the Practice of Medicine" (English translation), vol. ii., page 626.

§ "Manual of General Pathology" (translated from the sixth German edition by Drs. Duyn and Seguin), page 550.

‖ *Loc. cit.*

(this is interesting, as epistaxis is common in the form of Bright's disease which is most commonly attended with retinal apoplexies), "those from the female genitals or from the stomach and bowels, rare; petechiæ appear upon the skin, and a scorbutic condition is sometimes developed about the gums." Dr. Sinclair has recorded* a very interesting case in which intermittent epistaxis appeared to be due to malarial influence and yielded to anti-malarial treatment. Surgeon-Major Porter read a paper last year at the Royal Medical and Chirurgical Society,† on Recurrent Hæmorrhage from the amputated stump of a patient who had formerly suffered from malarial affection. Each attack of hæmorrhage was ushered in by a cold and hot stage resembling ague.

It will be seen that the majority of, though not all, writers who have described hæmorrhages into the brain and other organs have been inclined to attribute them to the melanæmia which has been so frequently observed in association with them. It has been held that the pigment cells, by blocking capillaries, lead to fluxionary extravasations or rupture. The retinal hæmorrhages observed in the case of ague I have narrated might, therefore, be naturally referred to the melanæmia which co-existed. I very much doubt, however, whether we should be justified in concluding that there was any direct or necessary connexion between the two.

Wishing to ascertain if retinal apoplexies were at all common in ague, I looked about for other cases. Mr. Atkinson was good enough to go to Greenwich Hospital to find out if there were any malarial cases there. He found six patients suffering from ague, and in two of these there were extravasations into the retina. A few days later I accompanied him to examine the cases. There were then only three out of the six cases remaining in the hospital, and of these two had hæmorrhages—they were the same two in whom Mr. Atkinson had previously seen hæmorrhages. These patients were all under the care of Dr. Ralfe, whom I must here take the opportunity of thanking for most courteously according me permission to examine any of his patients and have drawings or other observations made. The examinations were made by the light of a candle, so that only gross changes could be well observed. In one patient, a male aged eighteen, suffering from tertian ague, there was one small hæmorrhage in the left eye a little above the disc; his blood contained no pigment. In the other patient, a male aged twenty-nine, suffering from quotidian ague, there were numerous large

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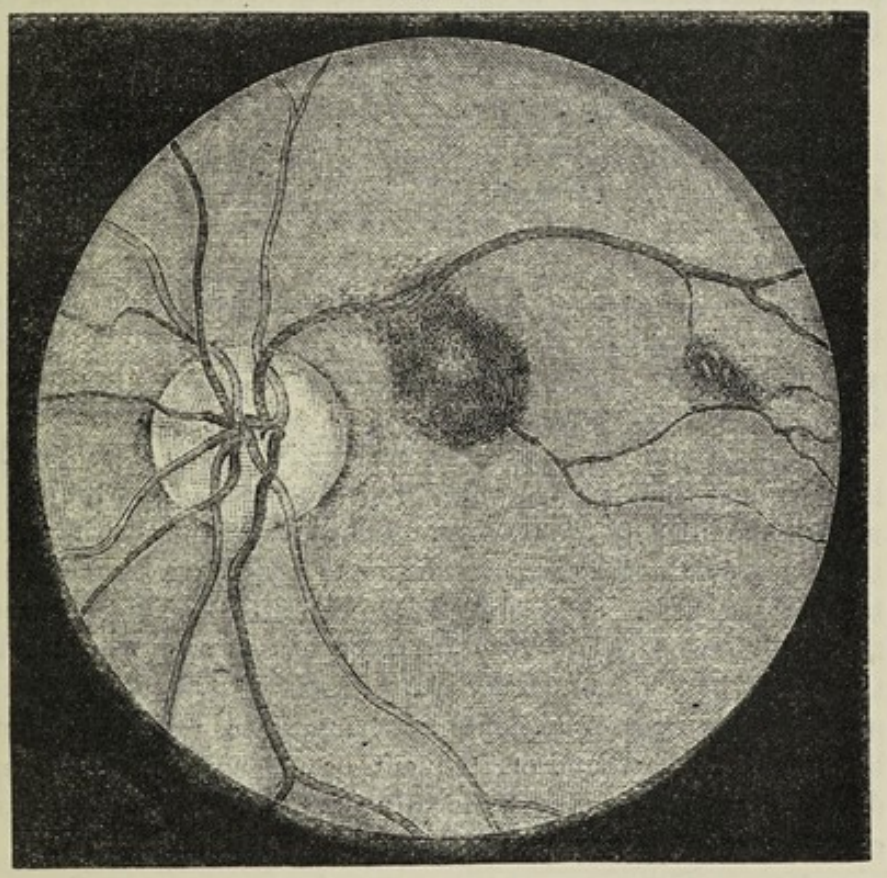
* *British Medical Journal*, October 28, 1876, page 551.

† *Royal Medical and Chirurgical Society's Transactions*, 1876.

superficial hæmorrhages in both retinæ; some of the hæmorrhages appeared to be clearing up at the edges, leaving white patches—one was paler in the centre than at the circumference; this patient's blood, also, was free from pigment. When Mr. Walker went to the Seamen's Hospital, five days later, to make a drawing of this patient's eye, the hæmorrhages had to a great extent cleared up, and he only found the two depicted in Fig. 2.

Now, these two patients had been on a vessel lying for some time off the coast of Mexico. There was in the hospital, also suffering from ague, a third seaman from the same ship. His

Fig. 2.



eyes and his blood were examined, but he had neither retinal hæmorrhage nor melanæmia. The form of his ague was irregular, so that he had the disease less severely than the other two patients.

This point—the stage or severity of the disease—appears to me to be of importance in determining the hæmorrhages; for it will be seen that of the three cases in which hæmorrhages were noticed, in the two in which the hæmorrhages were well-marked the ague was of the quotidian type; in the other case, in which there was only one small hæmorrhage, the ague was tertian. In the shipmate of the two patients at Greenwich, who had no hæmorrhages, the ague was irregular.

Moreover, the other cases examined by Mr. Atkinson, and found to be free from hæmorrhages, were patients about to be discharged cured from the hospital. In the few chronic malarial cases I have examined I could find no extravasations. If, therefore, retinal hæmorrhages are at all frequent concomitants of ague it would seem that they may be expected to be found in the early stage of the affection, when the disease is most active and the paroxysms occur at short intervals.

It should be stated that none of the patients in whose eyes I have found hæmorrhages complained of loss of sight or any ocular trouble. This shows the importance of the routine use of the ophthalmoscope in medicine, as so strongly insisted on by my colleague Dr. Hughlings-Jackson.* In Galezowski's case it will be observed there was defective sight.

As to the cause of the retinal hæmorrhages, I should conjecturally refer it to an altered condition of the blood. Retinal hæmorrhages are found in pernicious anæmia,† leukæmia,‡ purpura,§ diabetes,‖ and several other diseases characterised by alterations in the blood.

It is an interesting fact that retinal hæmorrhages have been described by Roth¶ in pyæmia, a disease which shares with ague, more almost than any other, profound alterations in the blood and repeated rigors.

Retinal hæmorrhages in connexion with ague may be much less frequent than would appear from the cases I have brought under the notice of the Society. I hope I shall not be thought to over-estimate their importance, or to generalise from one or two chance cases. I merely wish to call attention to the fact that they have been observed in three cases, and would ask those who have the opportunity to examine with the ophthalmoscope the eyes of patients suffering from ague. Should hæmorrhages be found of frequent occurrence, they may in doubtful cases have diagnostic value, as have the intraocular changes in Bright's disease and diabetes.

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* "A Physician's Notes on Ophthalmology," *Royal London Ophthalmic Hospital Reports*, vol. viii., part 4, 1873, and vol. viii., part 1, 1874; and elsewhere.

† Immerman, *Deutsche Arch. f. klin. Med.*, 1874, xiii., pages 209-244. Manz, "Veranderungen in der Retina bei Anæmia progressiva perniciosa," *Centralblatt f. d. med. Wissensch.*, 1875, No. 40, page 675.

‡ F. Poncet, "Rétinite Leucocythémique," *Arch. de Physiol. Norm. et Path.*, 1874, page 496. Liebreich, Galezowski, and most ophthalmic writers mention it.

§ Ruc, *Union Méd.*, 1870, No. 48. Wickham Legg, "Report from the Post-mortem Room," *St. Bartholomew's Hospital Reports*, 1875, page 64. Author, *Medical Times and Gazette*, March 3, 1877, page 233, and March 10, page 258.

‖ Leber, *V. Graefe's Archiv*, Band. xxi., Abth. 3, who gives the literature of the subject.

¶ *Deutsche Zeitschrift für Chirurgie*, September, 1872, page 471.

The second point of interest in the case I have read is the occurrence of melanæmia.

Melanæmia, long observed in malarial affections, has had its interest and importance greatly increased by some recent researches by Lanzi and Terrigi.* An abstract of their papers has been made in the *Centralblatt für die Medizinischen Wissenschaften.*† A translation of part of this I will quote: —"After extensive examinations of the microscopic fauna and flora of the marshes in the Roman Campagna, and of the Pontine marshes, Lanzi was led to the discovery of a peculiar alteration which the algæ undergo in these localities. Dark granules are found embedded in the endochrome or chlorophyll of the algæ cells, sometimes single, sometimes in clumps. They become more abundant as the algæ die, and, finally, they so completely fill the algæ cells that the latter no longer appear green but black; whilst, simultaneously with these changes, the algæ become stinking and decomposed. This process (which has been closely followed by Lanzi in his aquarium) takes place on a large scale each year in the Roman Campagna. The swamps which form in the winter are covered in the spring with a very abundant growth of algæ. In the summer, when the water dries, large surfaces of the country are covered with a continuous layer of decaying algæ. In the autumn, also, they die and decay on the surface of any water that remains, and the soil of these shallow marshes is transformed into a layer of decomposing slime, in which the microscope reveals the presence of the above-mentioned dark granules. These dark granules arising from the decomposition of algæ and other plants are, according to Lanzi, of the nature of a ferment. They are found abundantly disseminated in the dust of the Roman Campagna, or can be readily developed out of it by cultivation. According to Lanzi these granules are identical with the pigmented *Spherobacteria* of Cohn, and the *Bacteridium brunneum* of Schroetter; and by cultivation he obtained growths of *Monilia penicillata* of Freis. The pigment-granules which are found in the liver and spleen of persons suffering from malarial cachexia are identical in their properties with these ferment-producing granules, developed out of decomposing vegetables; and Lanzi strongly maintains the identity of the so-called 'malaria-melanin' of pathologists with the granules resulting from decaying plants. He has been able by cultivation to grow zoöglea-like vegetation from the pigment of melanæmic livers.

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* M. Lanzi e G. Terrigi, "Il Miasma palustre." 1. M. Lanzi, "Il Miasma palustre"; 2. G. Terrigi, "Nuovi studi ed esperienze sul Miasma palustre o sull' Agente fibrigeno." Roma, 1875. 27 s. 4°.

† 1876, No. 40, s. 713.

"Terrigi found abundance of 'malaria-melanin' in the liver and spleen of guinea-pigs which were made to breathe marsh-air containing the organisms described."

Lanzi and Terrigi would, therefore, regard the pigment found in the blood in melanæmia as the germs causing ague and other manifestations of malarial poisoning, and as taking their origin from the pigment-granules found in decaying algæ. This is a most important point as regards the pathology of malarial affections. Others, as Salisbury,* Balestra,† Hannon,‡ Bartlett,§ and Safford,‖ have claimed to have found in algæ the active principle of marsh miasm, the *contagium* of malarial diseases. But they have not observed any connexion between the algæ and the melanæmia so common in severe or pernicious forms of malaria.

Heretofore, the pigment-granules which have been noticed by observers of all nations in the malarial diseases of all countries have been referred to alterations in the blood. It has been generally held that an extensive destruction of the coloured blood-corpuscles takes place with the formation of the brownish-black granules from the altered and carbonised hæmatin. It has been thought that the greatest destruction of blood-corpuscles takes place in the spleen—an organ which always shows implication in malarial affections—and to a less extent in the liver, in the lymphatic glands, and in the medulla of bones. Blood drawn from the spleen during life or after death generally is found to contain pigment, whilst the organ itself is of blackish colour—the *milze nera* or black spleen. Blood passing from the spleen has necessarily to traverse the liver, where much of the pigment becomes arrested in the radicles of the portal vein, and produces the pigment liver (*pigment-leber*) so well described by Frerichs. The pigment which is unarrested in the liver, and escapes the meshes of the pulmonary capillaries, passes into the general circulation, and is distributed throughout the system. It has been found in all parts of the body. It is, when melanæmia is present, always found in the skin. It is particularly well seen in the brain, which, from its colour and vascularity, renders the presence of the pigment very conspicuous. Dr. Hammond has observed its presence in the retina during life.

The pigment, however produced, is generally found in one of three conditions—

1. Free pigment. This, though found in all parts, has been particularly observed in the bloodvessels of the spleen

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* *American Journal of Medical Science*, 1866, page 51.

† *Compt.-Rend.*, lxxi., No. 3, page 235, 1870.

‡ *Journal de Méd. de Bruxelles*, 1866, page 497.

§ *Brit. Med. Journal*, 1873, page 54.

‖ Mentioned by last author.

and liver. In early or slight cases the pigment is found as small brown or black granules. The coalescence of these appears to give rise to the larger masses. When recently formed they are made paler by the addition of acids and caustic alkalies; the older pigment-granules resist for a long time the action of these reagents. Dr. Hammond, in the paper already alluded to, depicts some large masses of irregular form obtained from the spleen during life by puncture with a hypodermic syringe. Frerichs, in his "Atlas of Liver Diseases" (Tafel IX. Fig. 2, *c*), shows some pigment masses from a clot out of the splenic vein.

2. Pigment-holding cells. These appear to be the most common form in which pigment is found in the blood. Meckel,* according to Virchow,† was the first to draw attention to pigment-cells in the blood, though Virchow himself appears to have been the first to recognise that the cells which contained the pigment were the colourless corpuscles of the blood. He writes—"The cells which I discovered in many respects bore a resemblance to colourless blood-corpuscles; they were spherical, but frequently also rather oblong, nucleated cells, within which a greater or less number of large black granules were to be seen." Meckel, Virchow, and Tigri noticed the association of the melanæmia with enlargement of the spleen and malarial poisoning. In Dr. Hammond's paper (handed round) the pigment-holding colourless blood-corpuscles are well seen, and they are shown in the drawing from the blood of my patient. Frerichs, in his Atlas, gives several illustrations of them. Colin‡ has drawn particular attention to the fact that the leucocytes are the carriers of the pigment, and that the deposition of the latter in perivascular spaces is to be explained by the migration of the corpuscles from the small vessels and capillaries. Heschl§ described very carefully the pigmentary alterations which are developed in the spleen, liver, and mesenteric glands in intermittent fever. M. Charcot‖ gave a most interesting and careful historical and

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* Meckel (*Zeitschrift für Pyschiatrie*, von Damerow, 1847) recorded the occurrence of melanæmia in association with marked pigmentation of the liver, spleen, and brain. The patient was a lunatic, and Meckel did not note the antecedence of intermittent fever. In a later paper (*Deutsche Klinik*, 1850, 50), Meckel showed that he then recognised the relation between melanæmia and malaria. Stiebel (Virchow's "Cellular Pathology") claims to have preceded Virchow in his description. Kelsch portrays in a lithograph very accurately the pigmentary changes in the blood.

† "Cellular Pathology," translated by Dr. Chance, p. 221.

‡ "Sur la migration du pigment sanguin à travers les parois vasculaires dans la mélanémie palustre" (*Gaz. Hebdom. de Méd.*, 1873, No. 3, p. 35). "Des rapports qui existent entre la pigmentation splénique et la pigmentation des autres tissus dans la mélanémie" (*L'Union Méd.*, 1874, No. 4).

§ *Zeitschrift der Gesellschaft de Aerzte zu Wien*, 1850.

‖ *Gazette Hebdomadaire*, 1857, p. 659.

critical *résumé* of what was known on the subject of melanæmia at the time of his writing in 1857.

3. Flakes (*Schollen*) containing pigment have been described by most writers. These are of irregular form and size, often three or four times as large as a normal colourless blood-corpuscle. Similar masses have frequently been met with in the urine in cases of melanæmia—so-called "melanuria." They consist of a basis of contractile protoplasm, embedded in which are the brownish-black or black granules of malaria-melanin. Frerichs* thinks these pigmented flakes are formed in the spleen, and are the broken-up fragments of coagula formed in the venous sinuses of that organ. In one case he was able to trace their formation to the liver. They must clearly, however, be formed at many different parts of the body, for they have been found in the vessels of the brain, kidneys, etc., and of such a size as to have precluded their having passed through the capillaries of the liver and lungs. Busch† has described these pigment flakes as having from two to six times the size of colourless blood-corpuscles. Frey‡ has alluded to them as granular lymphoid cells, having often a large increase of volume, containing granules of pigment. They have been attributed by Fuhrmann§ to the coalescence of the nuclei and granules resulting from the destruction of colourless corpuscles, which, according to him, is a constant feature in ague, and determines the occurrence of the paroxysms. Frerichs has, in addition to these flakes, described and depicted spindle- and club-shaped epithelial (endothelial) cells, which he regards as the detached epithelium of the lining membrane of the sinuses of the spleen infiltrated with the decomposed red matter of the blood.

Seeing the importance attaching to melanæmia in malaria, we are led to inquire, how often is this condition of the blood present? Here authorities differ. In the experience of some, it is very common; in that of others, of very variable frequency. Kelsch, in his exhaustive article on the Alterations in the Blood in Malarial Affections,‖ states that he found it in every one of twenty-four patients suffering from pernicious fever, whose blood he examined for this purpose. And of forty-seven cases of cachexia in which he examined the blood, in twenty-one he met with negative results, whilst in twenty-six he found melanæmia present. Of these twenty-six cases he

* *Loc. cit.*, p. 324.

† V. Busch, S., "Ein Fall von Melanæmia." *Œsterr. Med. Jahrb.*, Heft 11, s. 233.

‡ "Das Mikroskop." Fünfte Auflage, s. 139.

§ "Beiträge zur Keutniss der Malariar-krankheiten. *Deutsche Militär-ärtzl. Zeitschr.*, No. 12, s. 635.

‖ "Contribution à l'Anatomie Pathologique des Malades Palustres Endemiques," Brown-Séquard's *Archives de Physiologie*, 1875.

found pigment in the peripheral vessels in several during life. He says "I am led to believe that the pigment is a constant and characteristic product of severe or long-continued endemic malarial affections." He elsewhere states that the pigment-granules are taken up by the colourless corpuscles in the same way that cinnabar artificially injected is, and that they gradually disappear from the circulation by being deposited in the tissues. Magnus Huss* states that he has almost constantly found melanæmia in cases of malarial cachexia observed at Stockholm. Frerichs† was led, from the investigations he made, to the conclusion that melanæmia was most frequently met with in quotidian or tertian agues, rarely in quartan: the apyrexia was often imperfect, and the disease manifested a tendency to assume a remittent or even a continuous type. Dr. Hammond appears to have found pigment in the spleen in all the cases he examined. Colin regards the condition as very common. Hertz says,† "It occurs less frequently in simple acute malarial fever than in the tedious, long-continued, or pernicious remittent forms, and in chronic infection and malarial cachexia. As we know very little positively with regard to the method of its production, it will probably be long before we can explain the circumstance that this condition exists in the blood of one individual, after a certain number of attacks of fever, whose number, length, and intensity bear no comparison with those which have been suffered by another similarly constituted person, in whom no pigment can be found; in fact, that in some subjects this condition is not developed even after prolonged illness." It is probable that slight grades may pass undetected, for the cachexia which marks the disease is very generally present; and this has been shown, in some cases at least, to depend on the presence of pigment in and around the cutaneous vessels from which it is deposited in the rete Malpighii. Probably the amount of pigment in the blood is variable and dependent on conditions with which we are not familiar, and that under ordinary circumstances, and when the disease is quiescent, the pigment is confined to the spleen. Kelsch states that it appears in the blood at the moment of the access of the fever. It would be particularly interesting if the periods of melanæmia are found to correspond with outbreaks of malarial symptoms. Lussana‡ holds that under ordinary circumstances the poison of malaria is confined to the spleen and portal circulation, and that it is only when it passes beyond these limits

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* Mentioned by Charcot, *loc. cit.*

† *Op. cit.*, page 634.

‡ Quoted by Dr. Lauder Brunton, *British Medical Journal*, 1876, vol. i., page 257.

into the general circulation that the phenomena of intermittent fever make their appearance.

In the few cases I have examined I have failed to find pigment in the blood in all except the case which I have related in detail. But from the rapid manner in which the pigment disappeared from the blood in this case—whether to reappear I know not, as the patient went to sea—I should be careful to examine the blood on more than one occasion if possible, and to look through several slides before deciding that there was no melanæmia. The presence of pigment in the blood has been observed for periods extending over some months.

That melanæmia, though a frequent consequence of malarial poisoning, may be independent of the pigment-granules derived from decomposing algæ is quite clear, however. It has been noticed in connexion with melanotic cancer;* and here the pigment in the blood is obviously derived from the local pigmentary disease, which in its turn must obtain its colouring matter directly or indirectly from the blood.

Further observations are wanted before we can decide whether the particles of brown or black pigment, or malaria-melanin, found in the blood and tissues in intermittents are the actual germs or ferment which give rise to the phenomena which characterise malarial diseases. Enough has been said to show the great interest attaching to the subject, and the importance of examining the blood in cases of intermittent fever.

I have purposely avoided discussing the germ theory of malaria, except in so far as it relates to melanæmia. I may add, however, that it seems to me the only rational explanation of the phenomena of the disease.

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* Copland's "Dictionary of Practical Medicine," vol. ii. page 828-32. Nepven and Nyström, *Centralblatt*, 1874, s. 505.

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