

ORIGINAL COMMUNICATIONS.

ON THE ANCIENT AND MODERN DOCTRINES OF CANCER.

By ALEXANDER HENRY, M.D.

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THE mutual diffusion of knowledge acquired by personal investigation and experience in regard to pathology and therapeutics is the principal object for which such institutions as the Medical Society of London have been founded. It is, however, instructive to occasionally call to mind what our forefathers did for the promotion of medicine; to bring forth from the records of antiquity the opinions of the old physicians, and, placing these doctrines side by side with those which the modern methods of investigation have led us to adopt, to consider how far we have made any real progress in the healing art.

On the present occasion, I propose to bring before your notice some of the ancient and modern doctrines which have been held regarding cancer; and in doing this, I shall chiefly confine my observations to certain points—the pathological nature of cancer, and the means of diagnosis of the disease.

I shall commence with a brief review of the doctrines held by the ancients regarding cancer.

Turning first to the writings of the father of medicine, we find him discountenancing, in brief and energetic terms, any resort to operative procedure, even in the early stage of the disease.

"It is better," he says, "not to treat those in whom occult cancers have been formed. For when treated they soon die; but if not treated, they live a longer time."*

In the writings of Celsus (book v, chapter 28), we find some remarks on the pathology and treatment of cancer, which shew that the ancients possessed an amount of knowledge of the subject that could not be surpassed by any one not possessing the aids which modern science has brought to bear on the investigation of the subject.

"Carcinoma," says Celsus, "generally occurs in the upper parts—about the face, nostrils, ears, lips, and the breasts of females. But it also arises in the liver or the spleen. Certain pricking sensations are experienced about the part, which becomes swollen, immoveable, and irregular; and sometimes it is also torpid. The veins around it are distended and tortuous, and are either pallid or livid; in some persons they are concealed from view: when the part is touched, sometimes pain is produced, in other cases not so: sometimes the part is not ulcerated, but is harder or softer than it ought to be naturally: sometimes an ulcer is added to all these symptoms: sometimes it has no peculiarity. . . . It generally commences with what the Greeks call *κακός*; then it proceeds to carcinoma without ulcer; then ulceration takes place; and from that a *thymium*" (fungating growth) "is formed.

"None of these can be removed, except the *cacoethes*; the others are aggravated by treatment; and the more so in proportion to the energy of the remedies. Some have applied caustics; others the actual cautery; others have removed the disease by the knife; but no medicinal treatment has ever been of avail. When the cautery has been applied, irritation has been produced, and the tumours have gone on growing until they have destroyed the patient; when excised, the disease has returned even after the formation of a cicatrix, and has produced death; and, on the other hand, by attempting no violent measures for the removal of the disease, but by employing only mild palliative remedies, many persons have been permitted to arrive at extreme old age.

* Ὀκείσοις κρυπτοῖς καρκίνοις γίνονται, μὴ θεραπευεῖν βέλτιον θεραπευόμενοι γὰρ ἐπιβλυσταὶ τάχιστα μὴ θεραπευόμενοι δὲ πλείω χρόνον διατελοῦσι. (Aphor. vi, 38.)

"No one, however, can distinguish a *cacoethes*, which is curable, from a cancer, which is incurable, except by time and experiment. Therefore, as soon as the disease is noticed, caustics should be applied. If the disease is relieved, and its symptoms are diminished, the treatment may proceed to excision and the actual cautery; if it be immediately aggravated, we may know that it is a carcinoma; and all acrid and violent remedies must be desisted from. If the ulcer has an even surface, rose cerate may be applied, to which has been added powdered shell, and some of the water in which a blacksmith has quenched his red hot iron. If there is an excrescence, the *squama crisi* (oxide of copper) is to be tried, as being the mildest of caustics; but only if no exacerbation is produced; if otherwise, we must be content with the above mentioned cerate."

These remarks of Celsus present several salient points, on which it will be well to pause for a few moments, and which will serve as texts for a brief notice of all that is known of the doctrines of the ancients on the subject of cancer.

In the first place, it is quite evident that the ancient physicians confounded tumours of various kinds under the name of cancer: and that they should do this, is not surprising, when it is remembered how far we even now are from being able, with our improved methods of diagnosis, to distinguish with certainty between a cancerous growth in its early stage and a so-called non-malignant tumour. It is worthy of remark, however, that Celsus seems to have had an idea that all the tumours which he described under the term carcinoma were not identical in nature, and to have been impressed with the conviction that the formation of an accurate diagnosis was absolutely necessary to the success of an operation. "It is impossible," he says, "to distinguish a curable *cacoethes* from an incurable cancer, except by time and experiment."

The means of diagnosis which Celsus recommends are remarkable. Destitute of the aid afforded by the microscope, having probably no idea of the doctrine of the constitutional origin of the disease, or of the cancerous cachexia on which much stress has been laid in modern times, and accustomed to confine his diagnostic signs to the appearances presented by the tumour itself, he recommends a test, the proposal to adopt which would scarcely meet with approval from the cautious surgeon of our days. "As soon," he says, "as the disease is noticed, caustics should be applied. If the disease is relieved, and its symptoms are diminished, the treatment may proceed to excision and the actual cautery; if it be forthwith aggravated, we may know that it is a carcinoma." The doctrine involved in this sentence is curious. Let us suppose ourselves in the condition of not knowing whether a certain tumour is malignant or mild. If, on applying tincture of iodine or some more powerful caustic, the tumour diminishes, we should, according to the Celsian doctrine, complete its extirpation by the knife; if, on the other hand, our applications tend to aggravate the disease, we should have the satisfaction of knowing that we have summoned forth the malignant activity of the cancer-germ, and that further treatment is of no avail. Happily, with all our imperfections, we possess less dangerous, though perhaps not always more accurate means of diagnosis.

It is interesting to find the ancient physicians generally agreeing in the doctrine of the non-curability of cancer. The opinions of Hippocrates and Celsus we have already quoted. Galen, indeed, who had more originality of thought and action than many if not most of his predecessors in medicine, to some extent admitted the possibility of a radical cure by complete excision; but even then the arteries must not be secured with ligatures, or the disease would return. ulceration had taken place, he disapproved of "burning. Paulus Ægineta regarded cancer as allowed only that it is possible, by the use of remedies, to prevent incipient cancer from of the Arabian physicians, as Serapion rather approved of excision; Rhazes

dance in operative procedures, and confined his treatment, in common with many of his class, to palliative measures. In more modern times, opinions as to the benefit derivable from operation have been divided. Ambrose Paré, it may be remarked, was averse to excision.

We will now pass on to an examination of some of the modern doctrines regarding cancer.

It will be remembered that, in the course of last session, a paper was read before this Society by Dr. Druitt, the object of which was to point out the impropriety of using the term "malignant". On most of the points which were so ably treated on that occasion, I shall have but little to remark.

Since that time, the Imperial Academy of Medicine in Paris has been engaged in a lengthened discussion on the pathology, diagnosis, and treatment of cancer. The opinions of the most eminent of the French pathologists and surgeons—Velveau, Robert, Amussat, Malgaigne, etc.—have on this occasion been brought prominently forward; and I shall take occasion, in the course of the remarks I am about to offer, to make reference to certain features in this important and instructive discussion.

The first point to which I propose to direct your attention is the nature of cancer. We have already seen that the ancients regarded cancer as a local disease; yet Galen evidently had some idea of its blood-origin when he forbade the securing of the arteries by ligature after operation. In more modern times, some authors, as Baron, Adams, and Carmichael, have ascribed to cancer a hydatid origin. Ponteau and Abernethy advocated the theory of the local origin of the disease, from blows; etc. This doctrine, however, needs no laboured refutation. Broussais, C. Wenzel, Breschet, and Ferrus, maintained that cancer is the result of an inflammatory action in the part. Dr. Hodgkin has advanced a theory of the cystic origin of the disease. Our views have, however, generally partaken of the humoral theory, which is nowhere better expressed, in relation to cancer, than in the following quotation from the work of Dr. Walshe.

"A certain constitutional state exists, and may continue to exist for a variable period, without giving functional evidence of its presence, although the blood and the solids in the body are specially modified. In consequence of local injury, or otherwise, exudation takes place: upon that exudation the constitutional state has impressed special attributes and tendencies; among these attributes ranks an intrinsic power of vegetation. This vegetating faculty of the exudation reacts on the system by constantly draining it of a portion of its nutrient materials: the progeny feeds on the parent organism, and the first phasis of evolution is accomplished. But the natural tissues have been so modified in properties by the constitutional state, that they are incapable of resisting the encroachments of the vegetative exudation, and hence become the seat of atrophous, ulcerative, and other modes of destruction. Discharges of various kinds still further drain the system of its blood. . . . Meanwhile, secondary alteration of the blood is effected; this fluid becomes the vehicle for the circulation through the system of elements possessed of a germinating force; these stagnate, are deposited, and new vegetations spring into life and activity." (*On Cancer*, pp. 189-90.)

I shall presently have occasion to compare this doctrine with another which may be enunciated regarding the origin and nature of cancer. In the meantime, this seems to be a convenient place for a few passing remarks on the theory of Mr. Simon, that cancer, *i.e.*, the local manifestation of the disease, is developed as an organ of excretion. Mr. Simon, in his lectures on *General Pathology*, says:—"Cancerous organs are distinctly new products—new developments of the organism; and they correspond to some new purpose. Locally, cancer is a new excretory organ. Under the name of some mysterious constitutional necessity, a tumour (in its typical form) tends essentially to excrete: just as distinctly as the healthy kidney. . . . The cells of the gland-cells; like the nucleated

cells of a mucous membrane, only to discharge themselves with their contents." He regards this as conclusive an argument, for the constitutional and purely constitutional origin of cancer, as any which he could adduce to shew the constitutionality of small-pox or gout.

Let us pause for awhile on this theory of Mr. Simon—that a cancerous tumour is essentially a secreting gland, by which something is eliminated from the blood. This theory of elimination, as applied to the local manifestations of disease, is one which has gained some amount of favour among pathologists; and it certainly, on a superficial examination, appears plausible. The manifestations of small-pox on the skin, and of scarlatina on the skin, throat, and kidneys, at first appear to be "efforts of nature" to throw off a *materies morbi*: they may be so. So might appear to be an open cancer, constantly discharging its cells. But if we look further, we meet with difficulties. Can we consider the effusions into large joints to be truly the results of an eliminative process? And, in like manner, the development of cancer in the brain, and in other parts of the body where it is difficult—indeed impossible—that eliminative action could be set up without imminent danger to life, certainly militates against the doctrine laid down by Mr. Simon.

Returning to the question of the constitutional origin of cancer, the principal evidence in favour of this view appears to be—1. The hereditary transmission of the disease—a fact which I believe to be sufficiently established by the statistics of those who have made observations on the subject: 2. The tendency of the disease to return, after its apparent removal by the knife: 3. The manifestation of the disease in several parts of the body at the same time: 4. The cachectic appearance which it induces. In Dr. Druitt's paper, these points, with others, were discussed, with regard to the question of their being absolute signs of a malignant tumour, and were justly shown not to be peculiar attributes of cancer. Tubercle, for instance, presents the characters of hereditary predisposition and tendency to multiple development; and, in the case of the recurrence, or even the outbreak of pulmonary phthisis, in females after delivery, we have some analogy to what occurs after the local extirpation of cancer by the knife.

Constitutional or blood origin, then, can only be regarded as an attribute of cancer in common with other diseases. That cancer does depend on what, in the present state of our knowledge, we are accustomed to call a constitutional origin or pre-existing diathesis, is, I think, placed beyond doubt by the fact of its hereditary transmission: and we cannot, except by supposing such a constitutional origin (often, at least, hereditary), account for the first local appearance of cancer, under the influence of even the most favourable exciting causes. But the nature of this constitutional or hereditary predisposition is another question. The determination of this point is most important in regard to treatment. The experience of surgeons is mostly in favour of early operation; and it is not an uncommon opinion that cancer is curable, or at least that the return of the disease may be deferred for a great number of years, if the disease be removed sufficiently soon. In the recent discussion in the French Academy of Medicine, several of the speakers expressed opinions of this nature. Thus, M. Leblanc stated that, "when the disease has not returned, it has been in cases where the tumour was recent, small, hard, and removed entire". M. Amussat would operate early in cases where there is marked evidence of hereditary tendency to cancer; and he believed such early operation to have a probability of success. Galen, it will be remembered, also insists on the necessity of early measures.

On the other hand, experience shows that, if operation be deferred, the cancer is almost certain to return either in the cicatrix of the wound made by operation, or in some other part or parts of the body.

Again, cancerous tumours are not always single in their development. One of the speakers in the discussion in the Academy of Medicine (M. Delafond) objected to the propriety of the term "return of the disease" after operation;

for he believed that several tumours often coexist with the external one. When we have evidence of this, it is judiciously laid down as a principle, that operation is useless.

It becomes, then, an important question to determine whether the manifestation of cancer can be so purely local as to give hope, not only that the development of the disease will be deferred for a long time by the use of the knife, but that the disease may be altogether extirpated.

In the preceding remarks, I have spoken of the constitutional origin of cancer in such a way as will doubtless have led to the supposition that I assume the correctness of the humoral doctrine. There is another view, however, which deserves our earnest attention, and for which I am indebted to some hints which have fallen from the President of this Society. He imagines, if I have rightly comprehended the expression of his views, that some local diseases, which we often regard as of blood-origin, depend in reality on some peculiar changes in the plasma of the part affected, by which the plasma is made a suitable nidus for the development of certain pathological products. This doctrine is very applicable to certain cutaneous diseases: and the question has occurred to me, how far it may explain the development of cancer.

This view differs from that which I have quoted from the work of Dr. Walshe, principally in regarding the cancerous taint as primarily extravascular, and called into activity on the application of some exciting cause; the blood possibly being at first healthy enough, and only becoming infected in a subsequent phase of the disease. The best, however, we can say on the subject is as yet little more than hypothesis: and I am therefore prepared to admit that the theory which has been advanced is deficient in evidence.

It may further be objected, that the simultaneous development of cancer in different parts shows its blood-origin: this multiple development, however, even supposing it to be primary and simultaneous (which is disputed) is scarcely an insuperable obstacle to the reception of the doctrine of a locally diseased plasma.

This idea of local extravascular origin is somewhat supported by the fact of the delay or non-recurrence of cancer when operated on in an early stage, as shown by the statistics of the French surgeons to whom I have referred, and of others.

If, then, there is any probability in the theory that cancer, in its early stages, is mainly a manifestation of a diseased state of the local plasma, we have a most encouraging ground of hope in regard to treatment. If we operate early, when there is a single tumour, and while the disease, as far as we can ascertain, is within the reach of the knife, we may expect that the disease may not return, or that its return will be checked for a number of years. In such cases, however, it may be objected, that the operation has not been performed on a cancerous, but on a simple tumour. This objection may be to some extent valid; but I shall have occasion to revert to the difficulty here referred to in speaking of one of the principal means of diagnosis which modern science has brought to our aid.

Leaving, now, the subject of the nature of cancer, let me offer a few remarks on its diagnosis by means of the microscope.

The over enthusiastic advocates of the microscope have laid themselves open to the charge of an excessive confidence in their instrument, and are very generally regarded as giving the indications afforded by it an undue pre-eminence over those afforded by other means of investigation. It is, however, no less true that some of the most eminent microscopists look on their instrument as an auxiliary only, strengthening the opinion they have formed from clinical observation, or confirming a doubtful diagnosis. Thus Dr. Hughes Bennett, in his classical work on *Cancerous and Canceroid Growths*, writes, in the preface, in the following terms:—

“The microscope alone—that is, independently of all

other kind of observation—can seldom determine, in the living subject, the presence or absence of cancer. At the same time, the author feels himself bound emphatically to declare, that he thinks it capable of being as serviceable to the surgeon, in cases of morbid growth, as the stethoscope is to the physician in cases of diseased heart or lungs.” At page 221 of his work he also says: “The only physical proof we can arrive at of the existence of cancer is by the microscope; not that this instrument is in itself capable, even in the most expert hands, of doing everything; but, conjoined with a knowledge of the symptoms, progress of the case, form, and appearance of the morbid growth, it offers us an additional and most valuable means of prosecuting our inquiries.”

In the recent debate in the Academy of Medicine, the merits of the microscope were freely discussed; and the general tenor of the observations there made was in accordance with the opinions just quoted from Dr. Hughes Bennett. M. Leblanc said that, in some cases, cancer-cells had not been found in tumours which he had considered malignant on account of their multiplicity, general diffusion, and tendency to return. He regarded the value of the microscope as more scientific than practical; it had, however, enabled him to determine the nature of tumours where examination by the naked eye has failed. M. Barth regarded the pulpy matter of cancer as sufficient in general for the purpose of diagnosis; but when this was small in quantity, he would call the microscope to his aid; not forgetting, however, that certain clinical characters are likely to be of value in determining the nature of the tumour. The microscope may here reveal the presence of the cancer-cell: but it does not follow that the cell is always present in cancerous tumours, for it may either have not been formed, or, when softening has taken place, it may undergo various changes of decomposition. M.M. Gerdy, Jules Cloquet, and Malgaigne, regarded the indications afforded by the naked eye as of more value than those afforded by the microscope; while M. Velpeau, though not altogether denying that the microscope might be of service in the diagnosis of cancer, attached far greater importance to clinical examination. M. Robert, on the other hand, considered that the microscope had determined the special characteristics of cancer, and that it afforded more certain indications than the presence of the pulp, or than clinical symptoms. M. Mandl regarded the microscope as useful in forming a prognosis as to the return of the disease after operation; for a cellular structure is more liable to be regenerated than a fibrous one. M. Delafond would not admit the cell as an essential element of cancer; but the microscope was valuable in confirming diagnosis, so far as it shewed the presence of some form of cell.

Such is an outline of the opinions on the diagnostic value of the microscope, expressed during the discussion in the Academy of Medicine: and I must refer you to the writings of Müller, Walshe, Lebert, Rokitansky, Hughes Bennett, and other pathologists, for the statement of their opinions.

The question as to the utility of the microscope resolves itself into two points: first, as to the absolute value of the instrument in diagnosing a malignant tumour; secondly, as to the existence of a specific cancer-cell.

On the first point, we have several conflicting statements: first, that in some tumours, of an undoubtedly cancerous nature, cells are absent: secondly, that they have been found in tumours of a non-malignant character: thirdly, that the absence of cells from a hard tumour shews it to be non-malignant. On these statements I can only briefly remark; first, that in undoubtedly cancerous tumours, as shewn by their softness, it is possible that the cells may have undergone a process of disintegration, though I doubt whether cells could not be found in some portion of such tumours; secondly, that cystic sarcoma, to which I suppose reference is made when it is said that cells are found in non-malignant tumours, has a great tendency to degenerate; thirdly, that we must remember that apparently simple tumours are known sometimes to assume a malignant

type, and therefore I scarcely see how it can be predicated of any one of them that it would not act in this way. After all, as I shall presently take occasion to point out more fully, the question of malignancy is a relative one; and, as cells are most liable to assume that state of action to which I would apply the term malignant, I think that the existence of cells in a tumour affords grounds for regarding it as either malignant, or likely to become so; while the negative evidence is only valuable so far as it shews the most obvious conditions of malignancy not to have yet been assumed.

As to the specific nature of the cancer-cell, I can only state here, that a consideration of the opinions of the microscopists to whom I have referred, together with the few observations I have been enabled to make personally, lead me to doubt whether there is a diagnostic cell. I should be guided more by finding cells in situations where they ought not to be; and if there is any cell more diagnostic of cancer than another, it is the large "parent-cell", with from three to five smaller ones within it. But the absence of such cells does not shew that the disease is not cancer.

In the preceding remarks, I have made frequent use of the term "malignant", on the use of which, therefore, a few remarks will be necessary. I quite agree with Drs. Walshe, Bennett, and Druitt, that the use of this term is objectionable, so far as it conveys with it the idea of incurability, and thus tends to discourage the surgeon; but still I think that, if we could dissociate from it the idea of *invariable fatality*, we might still use it as expressive of a certain pathological condition—that, namely, in which a morbid growth is monopolising rapidly the nutritive material intended for building up the normal structures of the body. As cell-growths have the property of rapid evolution and nutrition, so far cellular structure may be synonymous with malignancy, but only so far as we find the destructive action in full operation. The term, as I just now observed, is probably, however, only relative; and some remarks made by M. Robert in the Academy of Medicine are so much to the purpose, that I must beg your attention to an abstract of them.

"The classification into benign and malignant is not in strict accordance with the teachings of histology. . . . The idea of benignity must no longer be associated with homœomorphism, nor that of malignancy with heteromorphism. Here has been the source of confusion; the barrier which has separated microscopists from clinical observers; raised, no doubt, by premature conclusions on the part of the microscopists, but strengthened by the adoption of the same faulty expression by surgeons. All tumours may be relatively benign or malignant. A true scirrhus, which lasts eight or ten years and more without ulcerating, without producing glandular enlargement, without causing pain or cachexia, and which, after removal, does not reappear, or only after some years, is extremely benign in comparison with an encephaloid tumour which runs through all its phases, and produces death in less than a year. And even a scirrhus tumour, such as has been described, is much more malignant than a large ulcerated glandular tumour. . . . The microscope cannot, any more than pathological anatomy in general, always determine the question of benignity or malignancy; but, in some cases, it teaches us to exercise caution; in others, it inspires us with a confidence amounting to apparent rashness."

I had intended to make some remarks on the prognosis of cancer in respect of operative treatment. This subject, however, I must defer for the present; merely remarking that we require most accurate statistics before the question of the efficacy or uselessness of operation can be entirely settled. On some future occasion I hope to be able to return to this subject, and to avail myself of the data furnished by the practical members of the profession.

12, Hinde Street, Manchester Square, April 1855.

NOTES ON OPHTHALMIC DISEASES.

By J. VOSE SOLOMON, Esq., F.R.C.S., Surgeon to the Birmingham and Midland Counties Eye Infirmary; formerly Honorary Surgeon to the Birmingham General Dispensary.

[Continued from page 846 of volume for 1854.]

FOUR CASES IN WHICH VIOLENCE TO THE EYEBALL CAUSED THE IRIS TO BE INVISIBLE, THE HUMOURS BEING TRANSPARENT.

A VIOLENT blow upon, or squeeze of, the eyeball, is sometimes followed by separation of the iris from the choroid, and multiplication or distortion of the pupil. Of these accidents Dr. Mackenzie has given, in the last edition (4th) of his *Ophthalmic Treatise*, illustrative engravings.

The Eye Infirmary of this town has afforded me opportunities of observing four adult cases, in which, as a consequence of violent concussion of the globe of the eye, the iris was rendered permanently invisible, the humours at the same time retaining their translucency. The records of the cases, though not so full as I could have desired, may not be without interest to the profession; for at present the annals of medical science afford only one parallel instance.*

Three of the cases occurred in males; one in a female. The *exciting cause* in one was an unskilful attempt to thrust the eye out of its socket by gouging; in three a violent blow on the organ.

Complications. In two, the case of the eye was ruptured; the sclerotica in one; the cornea in another. In two no fracture took place. In the case in which the sclerotica was cracked, the anterior chamber was noticed, three days after the accident, and when first seen by me, filled with blood. In the others, no internal hæmorrhage was detected. In one, the choroid, in place of its usual black reflection, had acquired a burnished copper appearance.

Vision. Two of the patients were completely amaurotic; a third could read half-inch letter; and a fourth type of the size of the leading articles in the *Times* newspaper.

CASE xv. A strong man, thirty years of age, a wholesale poulterer by trade, while engaged in a drunken row, had an attempt made upon him, by a person with whom he was quarrelling, to force out his right eye by thrusting the thumb between the inferior part of the globe of the eye and the osseous orbit. This "gouging" was not completed; but the sight of the organ was at once extinguished, and considerable pain was excited therein. For these symptoms, the patient, who was of dissolute habits, applied four leeches; and, in about a fortnight after the accident, he came to me at the Eye Infirmary. I noted that the whole front interior of the eye appeared of a dark bluish-black colour (invisible blue?); no vestige of iris could be anywhere traced; there was one vast pupil, bounded by the margin of the cornea; the latter membrane was transparent: with the exception of fading patches of ecchymosis in the ocular conjunctiva, the outer textures appeared normal; the eye was completely insensible to light. Upon looking obliquely into the cavity of the eyeball, the choroid was seen of a metallic lustre, exactly resembling burnished copper plate; the appearance was abruptly terminated in front by an extremely narrow ring—say two-fiftieths of an inch wide—situated in the position of the corpus ciliare, which I presume it was.

The patient did not present himself again for inspection. [A few months before this case came under my notice, an infant at the breast, only a few weeks old, was brought to me from Stone Street, Dudley, in whom the same appearances, as regards absence of the iris, colour of the pupil, and the appearance of burnished copper in the place of black pigment, were observed in both eyes as a *congenital* defect. The child was not amaurotic: it died of convulsions before attaining the age of six months.]

CASE xvi. A healthy Irishwoman, twenty-eight years of age, received a back handed rap upon the left eye from her husband, "all in play", as she good-naturedly said. Three days after the accident, she presented herself at the Eye

* A case by Mr. Dixon, in the *Lancet*.