exactly analogous to fatty degeneration of the heart, which is most extensive in fatal cases in the acute stage, but is only relatively slight or absent in cases surviving this stage. Mouravieff²⁸ in 1897 investigated the subject experimentally and found that in the acute stage there were marked degenerative changes in the motor cells of the spinal cord and that in animals surviving this stage degeneration was unlikely to be seen. Crocq²⁹ had previously in 1895 found similar changes. Rainy³⁰ in 1900 also found experimentally acute changes in the spinal motor cells. In 1902 I examined³¹ the neuro-muscular mechanism of the heart in 11 cases of acute diphtheria in Dr. F. W. Mott's laboratory at Claybury. In all 11 cases I found acute degenerative changes in the medulla oblongata, the motor nucleus of the vagus being affected, and in all the 11 cases there was extensive fatty degeneration of the heart. The vagus nerve was normal in every case. In two cases which died from asphyxia and showed practically no symptoms of systemic intoxication I found only occasional and slight changes in the central nervous system and cloudy swelling of the heart muscle. In conjunction with Dr. S. H. Bown, resident medical officer at University College Hospital, London, I am now repeating this piece of work experimentally and so far our results confirm those of Crocq, Mouravieff, Rainy, and others. Degeneration in the vagus nerve, although it does not occur in the acute toxic stage of diphtheria, occurs in the paralytic stage and was described as early as 1879 by Schech.³²

To sum up the present state of our knowledge with regard to the chief pathological changes in diphtheria it appears that as a result of the action of toxin there are produced fatty degeneration and cloudy swelling of various organs of the body, especially of the heart, and acute degeneration of the cells of the lower nerve centres; that after the acute stage of the disease has passed degeneration in the peripheral nerves occurs as a result of the action of toxone; and at this stage fatty degeneration of the heart and degeneration of the nerve cells are less likely to be prominent features but that interstitial changes are liable to be found in the heart.

In conclusion, it is seen from the clinical aspect that death in acute diphtheritic toxæmia is due to primary heart failure and to account for this extensive fatty degeneration is found in the heart and acute degeneration in the motor nucleus of the vagus. It cannot be definitely stated whether the acute changes in the vagus nucleus would produce irritation or paralysis of the vagus. It is, however, quite likely, as all stages of degeneration are found at the same time, that both irritative and paralytic effects may be felt by different portions of the heart at the same time and that in some cases an irritative effect may preponderate whilst in others a paralytic effect may be chiefly evident. The probability is that irregularity of action would be the prominent feature, that this irregularity would be subject to great variations in degree, and that in some cases a slowing of the pulse might be expected and in others an increased frequency. Such a lesion would also be quite likely to lead to vomiting. The cardiac dilatation is the result of weakness of the heart wall. The irregular pulse and fatal syncope of acute diphtheritic toxæmia are therefore due to the disturbed innervation of an acutely degenerate heart. The heart failure exhibited in the acute stage by patients who recover is probably the result of similar though less extensive changes. At a later stage of the disease the results of these changes, together with interstitial cellular infiltration, are sufficient to produce a latent weakness of the heart which can be brought into evidence by some strain and in this stage, also, degeneration of the vagus nerve probably plays a not unimportant part.

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Devonshire-street, W.

THE CANCER PROBLEM.¹

By J. BEARD, D.Sc.,

UNIVERSITY LECTURER IN COMPARATIVE EMBRYOLOGY, EDINBURGH.

IN the following simple story the correctness will be assumed of all the conclusions as to the etiology and nature of cancer which were advanced in, for example, the abstract of my lecture on the Problems of Cancer published in THE LANCET of Oct. 29th, 1904. The appended classification of neoplasms, an extension and inclusion of the "embryomata" of Wilms, may serve to make clear what in this paper a malignant tumour is defined to be.

1. *Embryomata*.—Benign neoplasms. Pathological manifestations of some greater or less portion of an embryo. They are composed of real tissues—that is, normal or somatic ("embryonic") cells or tissues. At its basis each is a greater or less portion of a twin, triplet, quadruplet, &c., identical with the individual containing it. They are not endowed with indefinite powers of growth and they nourish themselves like other normal tissues.

2. *Amphimixiomata*.—Malignant neoplasms. Combinations of embryomata and trophoblastomata. Pathological manifestations or attempts to reproduce the whole life-cycle including trophoblast and embryo. They are transitional forms. (The mixed tumours of Wilms are not all malignant, some being merely embryomata.)

3. *Trophoblastomata*.—Malignant neoplasms. Pathological manifestations of the asexual portion (trophoblast) of the life-cycle and sometimes, whether or not always is not at present known, attempting to repeat the germ-cell portion of the life-cycle, as shown by the researches of Farmer, Moore, and Walker. They are not known to differentiate actual functional gametes, eggs and sperms. They never include or repeat any part of an embryo. They are never composed of somatic ("embryonic") cells, though they may mimic such or even resemble no other cells in the body. As Sir James Paget pointed out long ago,² they are "imitation issues." They exhibit powers of unlimited growth and increase and they nourish themselves by eroding and destroying normal cells and tissues in a manner exactly like that of the trophoblast of normal development.

To illustrate the points to be considered I have put out certain microscopical preparations of transient ganglion cells, parts of the asexual generation of a dogfish. These may be taken to typify the trophoblast of a mammal or the cells of a malignant tumour. The preparations show: (a) cells in full functional activity prior to the critical period, and (b) cells which with the passing of the critical phase have entered upon their long, slow course of degeneration

¹ An abstract, with sundry subsequent alterations and additions, of a paper read before the Edinburgh Pathological Club on Dec. 13th, 1904.

² The designation of a malignant neoplasm as an "imitation tissue" was first used by the writer about a year ago in an address to the Edinburgh Pathological Club. The clear recognition of the existence of such "imitation tissues," as well as of the close resemblance, amounting to identity, of benign tumours to normal tissues, will, however, be found in Sir James Paget's classic work, "Lectures on Surgical Pathology," third edition, 1870, pp. 382 and 387. This book is a veritable treasure-house of valuable information. History does indeed repeat itself and, according to Virchow, in 1815 Fleischmann explained that the tumours were "nur Kopien normaler organischer Theile eben desselben Leibes, in welchen sie hervorgehen und bestehen." The authority of J. F. Meckel, according to Virchow, prevented the acceptance of this most important conclusion; indeed, this anathema has persisted or been renewed since that time, for to-day (1905) the conclusion, rightly drawn by Fleischmann 90 (!) years ago, is not accepted, so far as I am aware, by any living pathologist. "Eppur si muove!"

by simple atrophy. It would have been preferable to exhibit preparations of trophoblast, but those made after this method some years ago are now faded. The facts in the two cases, the mammal (sheep, pig, and others) and the fish (scyllium, raja, and others), are, however, quite similar. There is, indeed, only one mode of development in vertebrate animals. Freshly made preparations of human trophoblast of, say, the fifth and ninth weeks of gestation would display the like bloom on the one side of the critical period and the same decay on the other. Such figures of mammalian trophoblast have, indeed, already been published in the writings of my friend Dr. J. P. Hill.

The question which I wish to discuss is one which interested me exceedingly some years ago, long before its significant bearings upon the cancer problem were obvious. In a nutshell it is this: Why do these and certain other cells of a fish development, like those of the mammalian trophoblast, go on flourishing for a certain definite portion of the early development, whilst the parts of the sexual generation, "the embryo," are unfolding, and then with an almost tragic suddenness commence to degenerate and die? What brings this remarkable change to pass, one which in human development is lacking, if "the embryo" be absent or very abnormal?

Cancer is an irresponsible trophoblast. The unfolding of an embryo would stay its growth just as the formation of the sexual generation ends the growth of a shoot of a flowering plant. How does "the embryo" bring about this result? It does not devour the trophoblast but it must produce something which, as was pointed out two years ago,³ brings the degeneration to pass. Only in ordinary chorio-epithelioma is the malignant neoplasm a persisting portion and derivative of the trophoblast of the immediately previous gestation. Any ordinary cancer or sarcoma is a new development of trophoblast, due to the attempt of a germ cell to start the cycle anew. Except in mode of nutrition this irresponsible trophoblast does not resemble normal trophoblast, but it often mimics the structure in which it lies or it is like no other organ or tissue in the body. In any and every mammalian (Eutherian) development there is the potentiality of a malignant tumour,⁴ chorio-epithelioma, and this danger exists until the degeneration of the trophoblast is an assured but not completed fact. As researches made some years ago, but never published, demonstrated, in the pre-critical period the staining of the trophoblast cells resembled that of the functional transient ganglion cells—with methyl-blue eosin they took on an exquisite blue stain. With the passing of the critical period the cells of the trophoblast, as Hill has shown for the bandicoot (perameles), no longer took on the blue stain but absorbed ever more and more the red eosin. The like change will be noticed in the transient ganglion cells of the fish; it is also seen in the merocytes of the yolk.

Rather less than two years ago I really commenced to work at the problems of malignant neoplasms from their embryological aspects. The starting point for research here was obtained from certain results of prolonged investigations into the mode of vertebrate development. From these it had been established beyond question that in the normal life-cycle of development in any of the higher animals there were two generations—an asexual one, the "larva" or phorozoon, and a sexual one, "the embryo"—that the former was mainly, if not entirely, represented in mammalian development by the trophoblast, and that in every normal development the trophoblast was suppressed by the sexual generation, its degeneration commencing at the critical period with the completion of all the parts of the embryo. For the past eight years it had been recognised that at the critical period a change in nutrition always occurred. In 1902⁵ the conclusion was advanced that cancer was an irresponsible

trophoblast, the continued and unbounded growth of which was favoured by the absence of an "embryo" or sexual generation.

At that time there appeared to be one hopeful outlook for cancer research along the lines of embryology. It was that in every normal development the trophoblast, which in the absence of a completed embryo might become a malignant tumour, chorio-epithelioma, was invariably suppressed and degenerated. The task was to find out how this came about. For there appeared to be good reason for the hope, if not for the sure belief, that the factor or factors which brought about this result in normal development might also be potent when directed against an irresponsible trophoblast or cancer. To find these factors would be the solution of a general scientific problem of which apparently cancer was but a special case. These factors have now been found and in consequence cancer ceases to be a problem for the embryologist. A scientific solution of a certain problem has been obtained; whether or not this be at the same time a solution of the cancer problem in its medical aspects would not be for the embryologist to predict. He can only guarantee the truth of the embryological findings and conclusions and maintain that these would remain, even though they should utterly fail when applied in the treatment of malignant tumours.

The change in nutrition initiated at the critical period in vertebrate animals, from fishes to man, is based in the commencing functional activities of the pancreas. This introduces an alkaline digestion by means of the pancreatic juice with its various ferments. But what of the pre-critical nutrition? There are many ways in which this might be investigated. One might examine normal trophoblast, cancer or sarcoma, blastoderm of a fish, such as the skate, cleaved eggs of an amphibian, or blastoderm of a bird, all these being in the main homologous structures or asexual generations. What is found to obtain in the one must hold good in the others, for there is but one mode of vertebrate development. In this direction, when dealing with the yolk and merocytes of fish development and with the mammalian trophoblast in past years, some results had already been obtained; and in taking up the thread anew one's thoughts naturally reverted to the chick blastoderm as a readily obtainable material. Then came the recollection that the work had already been done for the chick and frog. In a recent publication Professor M. M. Hartog⁶ writes (p. 587): "One thing is clear as the result of this; all probability henceforward is in favour of the view that in the animal, as in the plant, a cell can only utilise its reserves secondarily and mediately—by the internal secretion of an enzyme." The author commences his paper by commenting upon the known facts that it has been shown in every case examined that in the utilisation of reserves in plants a ferment or enzyme is always present, which in suitable circumstances can effect *in vitro* the same process, usually of hydrolysis, which the living organism performs. He next proceeds to demonstrate that in the early development of animals, in the cells of the frog's egg in which cleavage is ended but no embryo yet present, and in the blastoderm of the three to four days' chick, there is a proteolytic ferment present. Under proper precautions this in acidulated solution (from 0.3 to 0.7 per cent. hydrochloric acid) gives the biuret reaction showing the presence of peptone. The reaction is absent in neutral or slightly alkaline solution. On p. 587 he arrives at the important conclusion that the digestion in the frog's egg (prior to the appearance of an embryo) and in the blastoderm of the chick (with the embryo removed) must be a purely intracellular acid one. For comparative and other reasons I now apply this conclusion to the trophoblast of a mammal and to the cells of a malignant neoplasm. No more than those of the trophoblast do the cells of a cancer contain yolk. None the less, in both the digestion must be the "ancestral" acid peptic (intracellular) one, characteristic of the asexual generation of a vertebrate, for this has been handed down as an unconscious memory from the time when the mammalian yolk sac contained food material. Recent researches, especially those of Vernon, have revealed the presence of traces of trypsin in many organs of the body. But this enzyme has never been, and cannot be, demonstrated in any malignant tumour. On the contrary, the work of Petry⁷ on many carcinomata and sarcomata has proved the

³ THE LANCET, June 21st, 1902, p. 1758.

⁴ So far as is at present known chorio-epithelioma does not occur in any mammal except man. The multiplicity of embryos in most other cases is against its happening. In almost every gestation in the pig, and often in the rabbit, there are abortive embryos from the trophoblast of which a malignant tumour might arise but for the presence and influence of the other embryos. In the course of the discussion the case of a full-time anencephalic human foetus was cited as against the validity of the conclusions advanced. In this the entire alimentary canal and pancreas were absent. A little cross-examination elicited the information that nothing was known as to its fetal membranes and that it was one of twins. The latter point is decisive in explaining how this monster had escaped the weeding out of the critical period. Had it been a single embryo, not a twin, it would undoubtedly have been aborted at the critical period and, moreover, hydatid mole or chorio-epithelioma would very possibly have followed.

⁵ THE LANCET, June 21st, 1902, p. 1758.

⁶ M. M. Hartog: Some Problems of Reproduction. II., Quarterly Journal of Microscopical Science, vol. xlvii., pp. 583-608, 1904.

⁷ Eugen Petry: Ein Beitrag zur Chemie Maligner Geschwulste, Zeitschrift für Physiologische Chemie, vol. xxvii., 1899, p. 398.

occurrence in these of a proteolytic ferment. From the author's account of his researches this is evidently of an (? intracellular) acid nature, like that recorded by Hartog for the chick blastoderm, &c. Petry's work is cited in the latest edition (1903) of Hoppe-Seyler's "Handbuch der Chemischen Analyse" (p. 387) as proving the presence of enzymes in malignant tumours.

In this connexion it would be of interest to cite some of the discussions upon "Extrazelluläre und Intrazelluläre Verdauung" and upon the enzymes or ferments in Verworn's "Allgemeine Physiologie" (p. 161 *et seq.*). In studying the history of the yolk sac of fishes I made many observations upon this question some years ago. At times one meets with cases in the yolk sac which are more "extracellular" than "intracellular." Ultimately, indeed, the latter passes into the former. In the sequel, therefore, the term "intracellular" will be used within brackets to indicate not so much its actual nature nowadays as its origin in past times from a real intracellular digestion occurring in the presence of yolk. In the chick or skate the yolk is contained in a yolk sac; in a frog within the cells of the cleavage. None the less, the ferment is the like one.⁸ The trophoblast of normal development, like the trophoblastoma of chorio-epithelioma, nourishes itself by an (intracellular) acid digestion. A malignant tumour, a cancer or sarcoma, nourishes itself in exactly the like manner. Like the trophoblast, it eats and erodes its way, destroying tissues by an (intracellular) acid digestion. Only by such could a cancer erode bone. To describe in detail what should follow would be to recite much of two papers⁹ published long ago as well as some other points noted since that time. The solution of the question is possibly the resolution of the problem of cancer. The mammalian embryo solved this ages ago; indeed, it "inherited" the solution from "ancestors" much lower down in the scale. The very existence of "the embryo" throughout the higher animals is dependent upon the suppression, the degeneration and death, of the asexual foundation upon which it came into being. In many invertebrata the sexual generation eats up (often by phagocytes) the asexual foundation or "larva"; and it must be recognised that in the higher forms it practically digests it. On the present occasion no account of the work required to establish it need be given; much, not all, of it is contained in my published memoirs. The fact may be stated briefly that in fish and mammal alike it is the commencing functional activity of the pancreas which initiates the degenerative changes in the asexual generation. At this epoch, the critical period, the fish commences to feed itself on yolk, not by an (intracellular) acid peptic digestion but by an alkaline pancreatic one. In some of the text-books of physiology stands the statement that the human pancreas at birth "contains trypsin and the fat-decomposing ferment but not the diastatic one (Zweifel)"; but, as I know from my comparative observations of years past, its activities really commence at the time the anus is formed, early in the seventh week of gestation, at a period when in the days of long ago the organism would have begun to digest the yolk of its now empty yolk sac. The pancreas functions throughout foetal life in a mammal though it has nothing to digest except the trophoblast.

During foetal life the pancreas is pouring out its secretion into an intestine which at the present day contains no food to be digested, for the food of the foetus has been prepared by the pancreatic digestion of the mother. To the foetus in utero this alkaline digestion is of no direct use but it has an indirect import in acting upon the trophoblast. The commencing activities of the pancreas during foetal life initiate an alkaline digestion by means of the most powerful and important of all the digestive juices, the pancreas. To

which of its ferments the observed results be due does not concern us. If the secretion be absent, neither the asexual structures of a fish development nor the cells of chorio-epithelioma do, or can, degenerate.

Under the conclusions already advanced regarding the nature of cancer as an irresponsible trophoblast, in consideration of the facts regarding the acid and eroding action of the trophoblast and of carcinoma, and in respect of the fact that in the absence of a completed embryo or foetus and its pancreatic secretion the trophoblast may become one of the most deadly of malignant tumours, chorio-epithelioma, it must be clear that nature itself has possibly provided a remedy for cancer and the pernicious (intracellular) cancerous digestion of the trophoblast in the secretion of that important digestive gland, the pancreas. This structure, I understand, is very rarely the seat of a primary carcinoma, and almost never of a sarcoma.¹⁰ Moreover, it is very important to note, that just as cancer is found everywhere in the vertebrata, just as there is one mode and one only of vertebrate development, so the pancreas and its secretion are a common heritage of vertebrate animals.

Briefly, as I conceive it, in normal development and in a malignant tumour the matter is simply a question of the victory of a stronger enzyme over a weaker one. In view of all this the events in a malignant tumour, such as, for example, the "heterotype" mitoses, lose much of their importance. They may still possess an interest for the cytologist and embryologist and even a passing one for the pathologist. But to the physician and surgeon these abortive attempts to form gametes cease in treatment to have any import whatsoever.

Practically all that was sought after from my own researches regarding cancer has now come to light. Embryologically, the problem of cancer has been to discover the antithesis of two enzymes and in particular to find out the enzyme capable of destroying a weaker one and thus of leading to the degeneration of the tumour by simple atrophy. The whole story is but another example of that antithetic alternation which underlies all the phenomena of living things. The solution of the problem of the functional relation of embryo and trophoblast, how the latter nourishes itself by an (intracellular) acid peptic digestion and degenerates slowly by a pancreatic digestion, becomes at the same time the embryological, if not the medical, resolution of the problems of malignant neoplasms, as well as of chorio-epithelioma. As an embryologist who is not a physician or surgeon my task is ended. The further applications of the scientific and theoretical solution of the problem may safely be left in the hands of those who know far better how to employ it. But they may not forget that in nature the degeneration and disappearance of these asexual structures, sometimes quick, are often exceedingly slow, though sure. Not that it is likely that the surgeon has removed his last malignant tumour but that, as one of the results of the work¹¹ begun more than 16 years ago, the physician has possibly had forged for him a light and not dangerous weapon, only second, if not equal, in potency to the surgeon's knife.

¹⁰ Two recently recorded cases of tumours of the pancreas may be cited. In the Berliner Klinische Wochenschrift, 1904, p. 479, Herr Ury "berichtet ueber einen Fall von Pankreas-carcinom mit Fett-Stuehlen, welche durch Darreichung von Pankreon wesentlich gebessert wurden," and in the Journal of Medical Research, Boston, vol. viii. 1902, pp. 385-95, A. G. Nicholls records a "simple adenoma of the pancreas." The first shows that the pancreas was not properly functioning, while the second, in which the tumour was not larger than a marrow fat pea, illustrates the difficulties encountered by tumours in this organ.

¹¹ Most of the work has been carried out in the University of Edinburgh, latterly with grants from the Moray Research Fund and the Carnegie Trustees.

⁸ It should not be forgotten that, as Verworn remarks (op. cit., p. 171) there exists a "ganze erdrueckende Fuelle von Enzymen." Hartog would seem to assume that the one discovered by him in the cleaved frog's egg and in the blastoderm of the chick, which must be common to the asexual generations of vertebrates, is the same as, for example, the enzyme of the mammalian stomach. It may be, but for present purposes it is not needful to insist upon this. Here it will be maintained that this enzyme of the blastoderm, trophoblast, or malignant tumour can only act in a slightly acid medium and that in all probability it is a much weaker one than that characteristic of the pancreas. The existence of the asexual enzyme and of the sexual one may account for the necessary existence of a gastric and an intestinal digestion. The sexual generation is of later origin in time than the asexual one, and its evolution has been bound up with that of a new digestive gland and enzyme, the pancreas, &c.

⁹ J. Beard: Certain Problems of Vertebrate Development, 1896, and the Span of Gestation and the Cause of Birth, 1897, both published by Dr. Gustav Fischer, Jena.

INTERNATIONAL SOCIETY OF TUBERCULOSIS.—A new scientific society has just been founded in Paris under the name of "Société Internationale de la Tuberculose." Its office is in Paris. Meetings are held monthly on notice from the general secretary. The scope of this association is the study of all questions concerning tuberculosis and the centralisation of means of defence. Its work will be published. The association is composed of medical men or men of science holding degrees or diplomas from French or foreign universities and colleges. Admission may be obtained by application to the president, which application must be accepted by a committee elected at a general meeting. The annual subscription is 10 francs (9s.) For further particulars and for applications address M. le Docteur Georges Petit, general secretary, 51, Rue du Rocher, Paris, France.