Book Reviews

CYTOLOGY AND CELL PHYSIOLOGY. Edited by Geoffrey Bourne. Clarendon Press, Oxford. XII + 296 pages.

In the Preface the Editor states that this volume represents an attempt to bring together chemical, physicochemical, and morphological aspects of the study of cells, and this has been carried out by selecting a number of subjects which are representative of different fields of the study of cells and which relate, as far as possible, one to the other. The subjects of the various chapters together with their authors are as follows: Technique for the Study of Cell Structures, by J. R. Baker; General Methods for the Physical and Physicochemical Study of Cells, by J. F. Danielli; The Monolayer Technique, by J. H. Schulman; Cell Membranes, by J. F. Danielli; Mitochondria and Golgi Apparatus, by G. Bourne; Nucleus, Chromosomes, and Genes, by M. J. D. White; Micro-Incineration, by E. S. Horning; Enzyme Systems, by H. Blaschko and W. Jacobson; and Pathological Cytology, by R. J. Ludford.

Since the central problem of cancer research is the investigation of the aberration of cellular functioning which determines malignancy, the topics discussed may be of general interest to cancer workers. Malignant cells are specifically discused in two of the chapters. E. S. Horning describes the present state of our knowledge concerning their inorganic constituents and R. J. Ludford contributes a brief review of their general cytological characteristics.

R. J. Ludford

BLOOD GROUPING TECHNIC. By F. Schiff and W. C. Boyd. Interscience Publishers, Inc., New York. 1942. 248 pages. Price $5.00.

This useful manual by the late Dr. Schiff and by Dr. Boyd gives in concise and readily understandable form the useful aspects of blood grouping. There is a succinct but satisfactory account of the various blood grouping methods, with a discussion of the M and N types. The material on the Rh factor is quite adequate. Of use to those interested is the section on blood transfusion, including as it does a description of the means of investigating transfusion accidents. The New York City regulations regarding blood donors and blood banks are given in full, as amended in 1939. A useful item for a second edition of the book would be the O.C.D. blood bank procedures.

An adequate section on the forensic aspects of blood grouping, with a discussion of disputed paternity, is given. There is also a description of the forensic application of blood grouping, including the study of blood stains.

In addition, a useful chapter is that on antigens similar to those of blood groups found in animals. A final section on the anthropological applications of blood grouping is clearly presented.

The reviewer feels that this book can be highly recommended to those who already have some fundamental knowledge of the problems involved in blood grouping and blood bank management.

Shields Warren

LE PROBLEME DU CANCER. By Charles Oberling. Collection "France Forever." L'Arbre, Montreal. 1942. 300 pages. Price $1.50.

The geneticist moves among his animals as though endowed with a spark of divine power, for he can determine the course of their lives even before they are born. He shows us strains bred for longevity, since by judicious matings over many generations he has eliminated all those weaknesses upon which disease could lay hold, and so can guarantee a life span of more than ordinary length. Then he shows us other strains that are resistant to cancer, and finally still others in which the disease will appear in all the members, at a certain fixed time and as inevitably as puberty or the menopause.

This abridged translation of one of the opening paragraphs in the section on heredity furnishes an example of the easy and entertaining style in which Oberling's book is written.

Avowedly for the layman, it can but sketch the general course of cancer research, and the specialist will therefore pass rapidly through the pages on theory, on transplanted tumors, and on the experimental induction of neoplasms, for their contents will be thoroughly familiar to him.

He may be tempted to pause, however, over some unusually felicitous passage such as the discussion of the role played by irritation in etiology. Infatuation with it has led to what might be called the hypnosis of positive cases, and to the total neglect of innumerable negative ones. Cancer is so relatively rare that it must be the outcome of an extraordinary coincidence of favorable circumstances, thus resembling somewhat the winning number in a lottery, and the irritation hypothesis accordingly becomes the hypothesis of chance.

That such diverse compounds as the carcinogenic hydrocarbons and aromatic amines, hormones, hydrochloric acid, sugar, and salts of zinc should elicit malignant growth may be explained by the supposition that they modify the tissues in such a way as to permit the intervention of an unrecognized carcinogen already present there. Certainly they do not achieve their effect by irritation alone.

From here the argument passes logically to a discussion on virus etiology, much the most interesting part of the book to students of cancer, for whether or not they are able to accept such an explanation they will admit that the evidence for and against this vexed question is presented fully, fairly, and entertainingly.

A long road has been traversed, says Oberling, since Borrel first suggested the virus hypothesis. Though the evidence available at that time was flimsy in the extreme, subsequent investigations have disclosed leukemias and benign and malignant growths due to virus infection, and the discovery of a papilloma of the rabbit and an adenocarcinoma of the frog kidney, both caused by viruses, has finally broken down the barrier arbitrarily erected between the tumors of birds and those of other species. Furthermore, and this is highly significant, it has been shown that a neoplasm may be caused by a virus and yet resist all attempts at its recovery. Thus it is no longer justifiable to deny the presence of virus in a tumor that cannot be transmitted by cell-free filtrates made according to current methods.

One characteristic of the viruses in particular is of the

greatest interest. They act almost instantly, whereas the other carcinogens so far recognized exert their effect only after a long preparatory period. These latter, then, seem to be indirect, whereas the viruses are direct, causes.

When we reflect on the diversity of all these agents we have the sensation of knowing at once too much and too little. Too much because instead of a single solution of the problem a whole series of explanations is offered; too little because of our profound ignorance of the cell, where all causes terminate. We occupy the position of one who is asked to explain the working of an automobile from its external appearance alone. He may analyze what is put into the machine to make it go, and what comes out of it, but he may not raise the hood. He may ignite or dissolve the vehicle to determine its total content of metals and combustible material, but that is all. How can he possibly form any idea of the motor, or of the thousand and one accessories essential to function? Yet the cell is infinitely more complex, and the derangement that we call cancer is hidden away deep in some inaccessible part of the mechanism.

Though the secondary, or extrinsic, causes are so many, they must be analyzed with the greatest care, for even though they be indirect complete familiarity with them would lead to prevention. Thus the radiologist says that roentgen cancer is caused by x-rays, and he knows that by taking suitable precautions he can prevent it; for him the question is settled.

But for the investigator in the laboratory the question is not settled. For him the x-ray is but an adjuvant to some other and still wholly unrecognized influence. For him, cancer is always the same disease, no matter what its secondary cause, for whether the malignant cell be found in fowl, rabbit, or man it has always the same features—exalted proliferation, invasive growth, and, above all, autonomy.

But what is the intrinsic cause? It must be: (a) carcinogenic; (b) present in every tumor; (c) compatible in its activities with, and explanatory of, all the secondary causes.

Radiant energy, parasites, and heredity may be eliminated at once, for they are not the cause of every cancer. There remain the carcinogenic chemicals and the viruses. Invariable presence is theoretically possible for either group, but if the carcinogenic compounds were the true cause they would be involved in the genesis of virus tumors and it would have to be admitted that the viruses in themselves are incapable of initiating cancer, acting only indirectly by forming carcinogenic chemical compounds. This contradicts facts already established, for the viruses elicit their effects more rapidly than the compounds they would elaborate.

Priority rests, therefore, with the viruses, but in assigning them this role we enter the domain of pure speculation. In examining the evidence for and against them we must see whether they fulfill the three postulates set forth above.

Discussion of the first is unnecessary, for many viruses are known that produce benign or malignant tumors.

The second postulate demands the constant presence of a virus in every neoplasm. Now if viruses are responsible for all tumors they would necessarily be concerned in the inception of those induced by chemical compounds, and the assumption would have to be made that every animal susceptible to these agents harbored the viruses of all tumors that might arise under their influence. This is not so unreasonable as it appears to be at first sight, for does not everyone carry in his digestive tract the colon bacillus and innumerable other organisms? What holds for bacteria ought to be true of viruses, the more so because these latter, obligate intracellular parasites as they are, lie sheltered from all the reactions that the body sets up against the bacteria. Nay more, do not the viruses furnish the best example of extraordinarily wide distribution, affecting all of certain varieties of plants and certain species of animals?

But here another difficulty appears. As the types of neoplasia are legion, and each virus elicits in general the same kind of tumor, there would have to be granted not only a wide distribution but a surprising multiplicity of viruses. Well, Nature has never been niggardly in such matters, and nothing is more amazing than the prodigious number of varieties included in certain species. Nearly 7,000 varieties of microbe take part in putrefaction, so why not allow a much smaller number of cancer viruses? In any case the total may not be so extravagant after all, for viruses may alter their cytotropism on occasion, those of fowl leukemia and fowl sarcoma, for example, giving rise to a wide variety of neoplastic changes.

If viruses are responsible for all tumors, why is it that they cannot be recovered invariably? Perhaps the effort fails because the virus has entered so completely into the economy of the cell as to become in effect an inseparable part of it; perhaps because the virus is so exacting in its demands that animals into which a filtrate is injected do not offer a favorable soil and thus the virus remains undemonstrable, even though present. Neoplasms that can be easily transmitted by cell-free extracts would then represent infections that are not too strictly conditioned, and it is highly probable that they are exceptions.

We come now to the third and last postulate, according to which the virus hypothesis must conform with all that is known respecting carcinogenesis, and here we shall examine the relation of viruses to cancers associated with parasitic infestation, carcinogenic compounds, and hereditary influences.

The effect of parasites is so inconstant that they alone cannot be a cause of cancer, and Borrel was therefore led to assume the intervention of a virus, relegating the parasite itself to the subordinate role of inoculator. The propagation of a virus disease by a parasite is no mere figment of the imagination, for recent investigations of swine influenza show that it does occur; hence the virus hypothesis is not inconsistent with the production of cancer by parasites.

The idea that a virus may be responsible for tumors that follow the injection of carcinogenic chemicals seems at first sight less plausible, and has been called even absurd. Yet recent investigations have brought out some singularly suggestive findings. For example, the virus of a rabbit papilloma, introduced into the blood stream, attacks the superficial epithelium only if this has been painted with tar or benzpyrene. In such a case it induces malignant transformation much more promptly than either one alone, and the carcinomas are more malignant than those following the application of tar or benzpyrene, for

these carcinogenic agents have sensitized the epithelium to the virus. Thanks to this and to other observations the intervention of viruses in the production of tumors by chemical compounds no longer seems improbable, and the virus hypothesis is not incompatible with the known facts.

As for inherited influences, cancer arises with extraordinary regularity in certain strains of mice, where it appears so inevitably determined by heredity that the mediation of a virus seems hardly conceivable. Actually, it cannot be excluded. No one will deny that susceptibility to some infections may be associated with hereditary characteristics, and if the virus of St. Louis encephalitis attacks certain mouse strains with perfect selectivity why deny the same property to a carcinogenic virus?

Furthermore, when it became known that maternal influence is much more effective than paternal in determining susceptibility to mammary carcinoma in mice, a mendelian explanation was no longer tenable. Borrel had already suspected that the assumed heredity might be connected with the passage of a carcinogenic virus from mother to offspring through the milk, and accordingly he exchanged newborn mice from mothers of cancer and noncancer strains. The outcome seemed to confirm his suspicion, though the data are difficult to evaluate because his strains were not truly homozygous. It has been fully substantiated, however, by more recent investigations upon unexceptionable material, and there is no longer any doubt that some factor of the highest significance, which affects the entire organism, is transmitted with the milk. Many believe it to be a virus, but the evidence is not yet complete. In any case the virus hypothesis does not contravene what is known of heredity.

A few matters still remain for discussion. The virus hypothesis is often declared unacceptable because cancer is not contagious. But neither are the leukemias and the filterable sarcomas of fowls, though each bird affected carries virus enough to infect millions of others.

Most of the objections, indeed, depend upon the outmoded idea that an infectious agent attacks indiscriminately and always, immediately eliciting its disease. Thus is it said that constant presence and wide distribution of cancer viruses would be inconsonant with the appearance of cancer at certain periods of life. It should be remembered, however, that some infections actually are conditioned by age. Ringworm of the scalp, for instance, is seen as a rule only in children and disappears promptly at puberty, but testicular atrophy creates anew a favorable soil. No chemist has ever discovered the changes taking place in the hair follicles under the influence of puberty; the fungus of ringworm is more knowing.

The only serious reproach to the virus hypothesis is that it is still unproved.

Most students of cancer therefore prefer an explanation less open to criticism, the hypothesis of somatic mutation. Its great virtue is that a way is left open for any etiological conception, since mutations may arise from causes the most diverse; its great fault, that it explains nothing. Somatic mutations, observed principally in plants and insects, are exceptionally rare in mammals, and those actually known affect secondary characteristics like pigmentation; they never bring about such an upheaval as the malignant transformation of a cell. Nor do cancers in general arise suddenly, as do mutations, but only after a long preparatory period of cellular derangement.

The cytological disorders that usually precede the appearance of cancer are hard to reconcile with the idea of simple somatic mutation. Many precancerous lesions include cells that appear to be already malignant, yet the true neoplastic change may be delayed for years. At what point in this process does the mutation occur? If at the end, of what sort were the preliminary changes? If at the beginning, not one mutation, but a whole series, would have to be assumed.

The most serious objection to the mutation hypothesis, in fact, is the existence of the virus tumors. For as viruses are able to initiate neoplastic growth much more rapidly than any other agent mutation need not be invoked to explain them.

To those who may be disposed to chide the author for a too enthusiastic partisanship he replies that it is never ill judged to be guided by a hypothesis so long as it does not do violence to the known facts, and that the best proof of its value is the amount of research to which it gives rise. Submitted to these tests the virus hypothesis has nothing to fear.

For him, as the Preface says, it is neither a preconceived idea nor yet a part of his medical background. Masson, his first teacher and a cytologist of note, always preferred a cellular theory, whereas Roussy had a horror of partisanship, and so ardent was his desire to retain the kernel of truth in every hypothesis that he was inevitably led to accept a plurality of causes and to seek the final cause in mutation. Borrel, on the other hand, was of a totally different temperament. He defended his ideas passionately in spite of everything, sometimes even against the evidence, and such seemed to his associates to be the case with cancer. Oberling, and many others, listened to his arguments, admiring his seductive eloquence and his fertile imagination, but without believing one single word of his tales about viruses that were ubiquitous and able to work their way along from one cell to the next until, at some auspicious moment, they encountered a susceptible one and ended by initiating cancer.

If the words of Borrel awoke no echoes it was because they were uttered at a time when it needed the greatest courage to maintain the virus hypothesis. Yet he was able to forsee that some experiments with spiroptera would have a negative outcome, that parasites might carry viruses, and that in the so called hereditary cancer of the mouse something other than hereditary influences must be transmitted. And more than once he was heard to say that it must pass by way of the milk.

Well, all these predictions have been realized, says Oberling, and one cannot help being impressed thereby.

But although the virus hypothesis does offer a plausible explanation for neoplastic growth, it is as a logical postulate rather than as an actual demonstration. The hypothesis is not in flagrant disagreement with the facts, though perhaps this can no longer be said tomorrow. Yet even though our conceptions should have to be revised almost overnight there would be the consolation, after all, that we are not seeking to confirm an idea but to solve a problem. In this quest all are likely to go astray, for, as Fontana wrote, in 1781, research is a game of chance in which the probability of error is great and that of discovering the truth small. WILLIAM H. WOGLOM