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SOME CHEMICAL ASPECTS OF THE CANCER PROBLEM[1]

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IN the lectures on chemotherapy I have attempted to bring out the importance of the study of the *selective* action of chemotherapeutic agents on specific cells. There is no doubt that the ultimate understanding of the mode of action of chemotherapeutic agents will depend on knowledge concerning the interaction between drug and cells, with particular reference to the physiological and biochemical changes resulting from this interaction. It is quite evident too that progress in this difficult field will depend on more extensive knowledge of the physiology and biochemistry of the cells concerned in the chemotherapeutic process.

To-day, I wish to discuss briefly certain chemical problems in cancer research. You may wonder what connection chemotherapy has with cancer research. In reply it can be stated that many phases of fundamental cancer research deal with the study of normal and malignant cells and their reactions to chemical changes in their environment. As in chemotherapy, some of these problems are concerned with the selective action of certain chemical agents on specific types of cells. In fact, I am convinced that work along these fundamental chemical lines holds out hope for a gradual solution of certain important aspects of the cancer problem. The purpose of the following discussion is to describe the experimental evidence upon which this belief is based.

For better orientation the subject can be divided into three topics: first, chemical carcinogenesis, that is, the transformation by chemicals of normal cells into malignant cells; second, the chemical characteristics of tumors; and third, attempts to cure animals with cancer by chemical treatment.

CHEMICAL CARCINOGENESIS

It has been known for a very long time that workers engaged in certain occupations or industries are apt to develop malignant tumors in certain organs. These

[1] Herter lecture, New York University College of Medicine, April 21, 1938.

so-called occupational cancers are frequent in chimney-sweeps exposed to soot, in workmen chronically exposed to coal tar, in spinners exposed to certain oils and in workers in dye factories. During the world war Yamagiwa and Ichikawa reported the first successful production of tar cancer in rabbits following the prolonged exposure of the skin to coal tar. This important observation at once raised the question as to whether the carcinogenic properties of coal tar were due to the presence in tar of definite carcinogenic chemicals. As is well known, the work of Kennaway, Cook and associates finally led to the isolation of 3,4 benzpyrene which is now recognized as the active carcinogenic substance in coal tar. It was easily shown that the prolonged application of a benzene solution of benzpyrene to the skin of mice caused malignant skin tumors. Now benzpyrene can be regarded as a derivative of 1,2-benzanthracene to which another benzene ring is attached. The English workers found that 1,2-benzanthracene had only feeble carcinogenic properties. However, the introduction of another benzene ring in the 5,6 position yielded 1,2,5,6 dibenzanthracene, which is quite active. In the course of a few years the English School synthesized a large number of related aromatic hydrocarbons for a systematic study of the relation between chemical structure and carcinogenic properties. There is no need of giving a detailed account of this extensive and painstaking investigation.

Perhaps the most significant observation made was the discovery of the powerful carcinogenic activity of methyl cholanthrene. This compound is a 5-methyl 1,2 benzanthracene containing a 5 carbon ring attached to the 6 and 10 position. A significant feature of the configuration of methyl cholanthrene is the similarity of its ring structure to that of a bile acid, namely, desoxycholic acid. In fact, Wieland first prepared methyl cholanthrene from desoxycholic acid by a four step reaction. This chemical relationship of the two substances suggested the idea that a pathological deviation in the bile acid or cholesterol metabolism might lead to the formation of methyl cholanthrene in the body and thus could explain the cause of some spontaneous malignant tumors. While this attractive hypothesis may still be true it has lost some of its probability due to the recent collaborative work of the Public Health Service with the Harvard Department of Chemistry. Fieser and his coworkers have synthesized a series of compounds which have been tested as to their carcinogenic power by Shear. It is perfectly clear that the 5 carbon ring, a characteristic feature of bile acids, is not an essential requirement for carcinogenicity, since the introduction of a methyl group in the 10 position of 1,2 benzanthracene is sufficient to endow the resulting compound with an activity of about the same grade as that of methyl cholanthrene. Lengthening of the carbon chain in the 10 position diminishes activity and shifting the methyl group from the 10 to the 5 position practically abolishes activity. It might be argued that methyl cholanthrene is formed from desoxycholic acid in the body to be degraded still further to 10 methyl 1,2 benzanthracene. The direct chemical conversion of methyl cholanthrene into 10 methyl 1,2-benzanthracene appears to be impossible, but whether this can occur in the animal body is another question. It is well to remember that the tissues can accomplish with ease chemical transformations which present-day chemistry has failed to perform in the test-tube. It is, therefore, still conceivable that a pathological bile acid metabolism may give rise to the formation of methyl cholanthrene or, still simpler, 1,2 benzanthracene, or possibly phenanthrene derivatives with high carcinogenic activity. A theoretically possible alternative would be the formation of similar carcinogenic substances as a result of a pathological course in the biochemical synthesis of sterols, since it is known that the animal body has the capacity to synthesize cholesterol and bile acids from simpler compounds. Progress in these directions will probably be slow and the foregoing remarks are intended to emphasize the value of the biological viewpoint in the study of chemical carcinogenesis.

Evidence relating the biological action of carcinogenic hydrocarbons and sex hormones was first put forward by Cook and coworkers, who discovered that 2,3 benzpyrene and 5,6-cyclo penteno-1,2-benzanthracene are mildly estrogenic. These chemicals, therefore, possess the dual activity of carcinogenesis and estrogenesis.

The first instance of the production of malignant tumors by a naturally occurring chemical of known structure was reported by Lacassagne. He showed that the long-continued treatment of male mice with large doses of estrin results in mammary cancer. This is a very significant observation, since Little reports that in over five thousand mice in his colony spontaneous mammary tumors occurred only in the females and not in a single male. Both Gardner and Loeb and their associates have clearly shown that the carcinogenic action of estrogens is proportional to the size of the dose. Furthermore, Gardner and coworkers made the paradoxical observation of the production of seven sarcomas in mice at the site of the subcutaneous injection of estrogens. In a paper which has just appeared they report the production of carcinoma of the cervix of the uterus in the mouse 319 days following the repeated subcutaneous injection of large doses of estradiol benzoate. This is in harmony with Loeb's previous observation of precancerous cervix lesions following estrogen injections.

The preceding account has dealt with carcinogens which have a chemical relationship to certain naturally occurring substances. Brief reference will now be made to chemicals which are completely foreign to the animal body, yet can induce malignant tumors.

2-amino-5-azotoluene is such an example. If a solution of this dye in olive oil is mixed with the diet of rats, malignant liver tumors are produced after about 10 months of such feeding. Shear has produced these tumors in mice by several subcutaneous implantations of the dye in solid form. Due to its low solubility this deposit is absorbed very slowly in the course of weeks. Tumor production is always accompanied by a great enlargement of the liver. The precancerous changes consist in necrosis followed by proliferation of bile duct epithelium and sinus formation. The malignant cells can easily be recognized as large cells surrounded by the smaller normal hepatic cells. These tumors have been successfully transplanted to normal animals, a fact which is additional proof of the malignant nature of these tumors. Dr. Emmart has succeeded in cultivating this tumor *in vitro* for prolonged periods. The interesting feature of the carcinogenic action of amino azotoluene is its selective action upon the liver after oral or subcutaneous administration of the dye. The high solubility of the dye in fats and lipoids may be a factor in this selective action.

In a recent paper it is reported that "butter yellow," an azo dye closely related to amino azotoluene, will induce liver tumors in rats. Confirmation of this claim would justify discontinuation of the use of this dye for coloring butter.

Another matter of practical concern is the recent production of bladder tumors in dogs by Hueper and his colleagues. The so-called "aniline tumors" of the urinary bladder in workers in dye factories have been attributed to chronic exposure to aniline, benzidine and betanaphtylamine. However, all previous attempts to produce this disease in animals by any one of these three aromatic amines had failed. Hueper gave dogs commercial beta-naphtylamine by mouth and subcutaneously in increasing doses over a period of about 1½ to 2 years. By periodic cystoscopic examination and biopsies it was possible to follow the histopathological process leading to the formation of benign papilloma and finally to true carcinoma. It is significant that the time required to produce these malignant tumors is very long. This is consistent with the belief that these bladder tumors in dye workers also require many years of exposure. Commercial beta-naphtylamine always contains impurities, and it is therefore still an open question as to whether the tumors were produced by these impurities or by the naphtylamine *per se*.

In this connection it is important to emphasize the use of chemicals of the highest purity, if the work is designed to incriminate a definite chemical substance as carcinogenic agent. For example, triphenylbenzene was reported a few years ago as having carcinogenic properties, but Shear failed to obtain tumors by using a very carefully purified product. Furthermore, tetraphenylmethane has been reported as a slowly acting carcinogenic hydrocarbon. In this case also it would be advisable to perform experiments with a product of the highest attainable purity.

Two compounds which produce tumors very slowly are 1,2,5,6 dibenzacridine and 3,4,5,6 dibenzacridine. The first of these two compounds is of particular interest, since it is analogous to the potent 1,2,5,6 dibenzanthracene, in which one of the carbon atoms in the meso position is replaced by a nitrogen atom.

A very interesting instance of a chemical possessing both chemotherapeutic and carcinogenic properties is a styryl-quinoline derivative, studied by Browning and his coworkers. Subcutaneous injection of this water-soluble compound has produced sarcomas in 10 out of 19 mice. The substance is also trypanocidal. A closely related substance is trypanocidal, but not carcinogenic. A third related substance apparently lacks both properties. These observations illustrate the remarkable change in biological properties brought about by relatively slight changes in the chemical configuration of a compound.

At a recent scientific meeting Hall and Franks reported the production of osteo sarcoma in animals following the repeated subcutaneous injection of relatively large doses of acetylcholine. This work is now being repeated by the Public Health Service. Needless to say that confirmation of the production of malignant tumors by acetylcholine would present an intriguing subject for further study, since acetylcholine is a naturally occurring body constituent with a very specialized physiological function.

This brief account clearly demonstrates that work of the last few years has brought forth evidence of the carcinogenic action of a great variety of chemical compounds. There is good reason to believe that further work will add many more active compounds to this already long list.

We may now pass to a review of the various factors influencing the production of chemically induced tumors. Of these the study of the dose and time factors have received some attention, though the available information is by no means as complete as would be desirable. The results obtained with subcutaneous injections of such highly active compounds as dibenzanthracene, benzpyrene or methyl cholanthrene into rats or mice indicate that within a certain dosage range increase in the dose shortens the time at which tumors

appear. Thus Dunning, Curtis and Bullock found that in inbred rats injected with 2 mg of benzpyrene the mean time for the production of tumors was 201 days, whereas with 16 mg the mean time was cut in half—to 102 days. A further increase in the dose did not cause a further decrease in the latent period. The shortest latent periods on record vary between 30 to 45 days. On the other hand, Shear reports the production of a transplantable sarcoma in a mouse 14 months after the subcutaneous implantation of as little as 0.4 gamma dibenzanthracene in the form of a cholesterol pellet. The most reasonable explanation of this interesting observation is based on the assumption of a very slow and gradual release of the active agent from the pellet.

As to the susceptibility of various animal species to chemically induced tumors the available evidence points to wide variations. However, it should be emphasized that for various reasons most of the experimental work has dealt with mice and rats. Almost every type of malignant tumor seen in man has been induced chemically in mice and rats. Recently Shear has even produced brain tumors in mice by the implantation of methyl cholanthrene. These tumors appear to be gliomas. Chickens are quite susceptible to induced tumors, whereas rabbits are relatively resistant. Guinea pigs also are resistant, yet Haagensen and Krehbiel report four fibrosarcomas and four liposarcomas appearing one year after the subcutaneous injection of 3,4 benzpyrene. As already mentioned, dogs respond to beta naphtylamine with bladder tumors, but they seem to be more resistant to the highly active hydrocarbons. However, it may be that the latent period for tumor production in dogs may be a matter of years, whereas in mice it is a matter of weeks.

Until recently it was believed that all mice were about equally susceptible to chemically induced tumors. But the work of Andervont, of the Public Health Service, has revealed a striking difference in the average time of appearance of induced tumors in different highly inbred strains of mice. In one strain, for instance, 0.8 mg of dibenzanthracene produced tumors in every mouse within 28 weeks after injection, whereas in another strain no tumors appeared until 40 weeks after injection.

A systematic investigation with 8 different pure strain mice has failed to reveal a consistent correlation between susceptibility to induced subcutaneous tumors and susceptibility to spontaneous mammary tumors.

In the foregoing discussion reference has been made to several instances of chemically induced tumors arising in a tissue removed from the site of administration of the carcinogenic agent. A further example is the production of liver tumors by the subcutaneous injection of 2-amino anthracene (Shear). Primary lung tumors have also been observed following the subcutaneous injection of dibenzanthracene into a certain pure strain of mice (Andervont). Many of these tumors appeared without the occurrence of subcutaneous tumors. This particular strain of mice has a high incidence of spontaneous lung tumors which appear relatively late in life, whereas the induced lung tumors occur much earlier. The most plausible explanation of this finding is that the dibenzanthracene, after absorption from the subcutaneous tissue, is carried to the lung where it accelerates the normally occurring carcinogenesis. This view receives support from the production of primary lung tumors by implantation of dibenzanthracene into the lungs of this mouse strain. It is of interest that the susceptibility to spontaneous lung tumors is inherited as a dominant factor. It would seem, therefore, that under certain circumstances the production of primary tumors of the lung may be attributed to the operation of at least two factors, first, an intrinsic hereditary susceptibility, and, second, an extrinsic chemical factor. This experimental evidence now serves as a basis for a comprehensive investigation by the Public Health Service of the causation of lung tumors, a problem which is of some concern in view of the apparent increase in the mortality from lung tumors in the population of this and other countries.

Parenthetically, it may be mentioned that some of the chemically induced primary lung tumors exhibit a typical adenomatous structure which on repeated transplantation of the tumors into other mice of the same strain changes to that characteristic of sarcoma.

Mechanism of Carcinogenesis

The production of malignant tumors by pure chemicals unquestionably represents a major advance in our knowledge of the causation of cancer. The next important problem is to explain how any one of these carcinogenic agents causes the transformation of normal into malignant cells. This question goes to the heart of the cancer problem and deserves intensive investigation from all points of view. At present the situation is quite obscure, in fact it is rather perplexing, because of the great variety of chemical carcinogens. From the purely chemical view-point it is utterly impossible to find a common characteristic of such diverse agents as the active hydrocarbons, estrine, aminoazotoluene, dibenzacridine, a styryl quinoline derivative, etc. Therefore, it is necessary to shift the interest to the study of the changes brought about in living normal cells under the influence of potent carcinogenic chemicals.

The outstanding biological characteristic of all malignant tumors is an apparently unrestrained capac-

ity for proliferation. Therefore, investigation has been directed to ascertain whether chemical carcinogens act as stimuli of cell proliferation. The results have been contradictory. On the basis of histological evidence Loeb believes that all carcinogenic agents induce a localized cell proliferation in susceptible animal species. Thus it has been shown that estrin in male mice stimulates the proliferation of mammary tissue. According to Gardner and coworkers small doses produce a normally appearing proliferation, whereas the large doses required for tumor production induce an abnormal proliferative response, evidence considered as supporting a direct carcinogenic action of estrogens on the mammary tissue. However, the view has also been advanced that this proliferation is brought about indirectly by the stimulating action of the sex hormone on the anterior lobe of the pituitary. This contention seems supported by the hypertrophy of the anterior lobe following treatment with large doses of estrine and the apparent increase in the incidence of spontaneous mammary cancer in mice by multiple transplants of the anterior pituitary lobe. In this connection it is interesting to note that Bagg has shown that the injection of extracts of the anterior pituitary, at certain seasons of the year, makes possible the induction of teratoma testis in fowl by intratesticular injections of zinc chloride.

A few attempts have recently been made to elucidate the action of carcinogenic hydrocarbons by studies on some lower organisms. Thus Hammett and Reimann have shown that methyl cholanthrene and dibenzanthracene do enhance the production of new growth in *Obelia geniculata*. Owen reports stimulation by dibenzanthracene of regeneration of cut segments in planaria, and Goldstein finds that the same agent stimulates the growth of a bacterium—*Escherichia communior*. It is obviously difficult, however, to utilize these observations for the explanation of carcinogenesis. On the other hand, it would seem that observations on tissue cultures have a more direct bearing on this problem. Therefore, Dr. Earle and I have carefully studied the action of highly purified methyl cholanthrene, prepared in Dr. Fieser's laboratory, on cultures of fibroblasts from the subcutaneous tissue of rats. The results obtained clearly show that methyl cholanthrene is highly toxic, since concentrations above one thousandth of a milligram per cc cause degenerative changes and the ultimate death of the cultures. Even extreme dilutions, such as two ten-thousandth milligram per cc, retard the growth rate of the cultures. It was impossible to detect the slightest stimulating effect under any conditions on the cultures. Subcutaneous injections of methyl cholanthrene into rats of the same strain produced a high percentage of sarcomas.

Haddow reports that the injection into young rats of one or two injections of about 10 mg of three carcinogenic agents, namely, 1,2,5,6 dibenzanthracene, 3,4 benzpyrene or 1,2,5,6 dibenzacridine, causes an immediate and prolonged retardation of growth, whereas three closely related non-carcinogenic substances failed to influence the growth rate. He also established the paradoxical fact that carcinogenic hydrocarbons injected daily in small doses inhibit the growth rate of transplanted tumors in rats.

Reimann observed that the combined application of parathiocresol and dibenzanthracene to the skin of mice lessened and delayed the incidence of skin tumors. This is of interest since thiocresol stimulates cell proliferation in the healing of superficial wounds. Therefore, consideration of the more significant results obtained with mammalian tissues would seem to indicate that at least some of the most potent chemical carcinogens do not act as stimuli for cell proliferation. Reimann is right in saying that stimulation of cell proliferation alone does not lead to neoplasia. Hence, the conversion of normal into malignant cells is probably due to profound metabolic changes, the nature of which are still obscure.

A few attempts have been made to change normal cells in tissue culture into cancer cells by exposure to carcinogenic hydrocarbons. The negative results obtained so far should not discourage further efforts in this direction, but we will have to keep in mind of course that conditions *in vitro* differ considerably from those prevailing in the animal body.

Practically nothing is known as to whether chemical carcinogens act as such, or whether they have to undergo chemical changes in the tissues before they acquire carcinogenic properties.

Finally, it should be mentioned that the proponents of the virus theory of cancer are inclined to regard chemical carcinogens as agents which merely render normal cells very susceptible to the action of ubiquitous carcinogenic viruses. Some of the arguments advanced in favor of this view are far from convincing because of incorrect generalizations. Gye in a recent address before the Royal College of Surgeons states that chemically induced tumors make their appearance after a much longer time than tumors induced by viruses. Yet in the same address it is said that the domestic rabbit strain of the Shope virus in domestic rabbits produces papillomas, nearly all of which become malignant within two years. It is stated furthermore that chemically induced tumors are confined to the site of application of the chemical. The production of tumors by chemicals in tissues distant from the site of application is ignored. The important observation of Rous and Kidd of the production of fulminating carcinosis at the site of the application of coal

tar to the skin of rabbits which are subsequently infected intravenously with the Shope virus, is again interpreted as showing that the tar merely prepares the ground for the action of the virus. This may be true, but is by no means proven. Both coal tar and Shope virus applied singly to the rabbits produce skin cancers after a long time. Is it so unreasonable, therefore, to assume that the action of the combination tar-virus may result in a summation or synergistic effect as evidenced by the shortening in the latent period for tumor production? Would a similar effect be obtained by the use of a non-carcinogenic tar or non-carcinogenic hydrocarbons in combination with the virus? How can the virus hypothesis explain the fact that the mere addition to, or elimination of a methyl group from, the ring structure of some hydrocarbons elicits or abolishes carcinogenic activity? Why are brain tumors found so seldom in the thousands of mice which have been kept under observation for long periods in cancer research laboratories (Slye, Holmes and Wells), while through the use of a few dozen mice such tumors have been induced chemically.

In short, it seems wiser for the present to admit our ignorance concerning the mode of action of carcinogenic agents, whether chemicals or viruses, in order to avoid unjustifiable generalizations. Speculations of course have their value, but this difficult problem will only be solved by further experimental work.

Chemical Characteristics of Tumors

A cardinal feature of all cancer cells is their progressive and apparently unrestrained proliferation in the animal body. It is pertinent, therefore, to inquire whether this peculiar behavior of malignant cells can be explained on a chemical basis. Here we meet at once with difficulties. In fact, the great amount of work done on this problem has rather emphasized the chemical similarity of malignant cells and the normal cells from which they arise. So far there has not been discovered a single qualitative difference in chemical composition. On the contrary, such highly specialized chemical functions as the production of specific hormones are retained by malignant tumors derived from hormone-producing glands. Whatever apparent chemical differences do exist are of a quantitative nature, and even in this regard there are exceptions to the rule. For instance, the well-known studies of Warburg on tumor tissue *in vitro* were supposed to distinguish malignant from normal tissues by the abnormally high aerobic glycolysis and defective respiration of tumor tissue. Cori and Warburg were able to show that venous blood from cancerous tissue contains more lactic acid and less glucose than other venous blood. We have extended these findings by showing that the lactic acid production of tumors in living animals following the intraperitoneal injection of glucose, fructose or maltose is sufficient to cause a striking decrease in the pH of the tumor, as measured by the capillary glass electrode. Under the same conditions the pH of such normal tissues as striated muscle and subcutaneous tissue was not changed. It is conceivable that the excessive amounts of lactic acid present in tumors, with the consequent decrease in pH, may be a factor favoring the necrosis of poorly vascularized parts of tumors, and is concerned in the destructive action of tumor cells on adjoining normal tissue.

In further work we have made some interesting observations on the relation of protein metabolism to tumor growth. It is obvious that the growth of malignant as well as normal tissues requires the synthesis of tissue proteins. The problem was attacked by a systematic study of the action of cathepsin in extracts of tumors and normal tissues. We found that the lytic activity of this enzyme is favored by anaerobic conditions. If, after a few hours of anaerobic digestion, the digests are oxygenated, the amino nitrogen decreases and the trichloracetic acid precipitable fraction increases by about 30 per cent. This we interpret as evidence of a reversal of proteolysis or protein synthesis. This synthesis is accompanied by a progressive decrease in the concentration of reducing substances in the deproteinized fraction, as indicated by a decrease in the iodine titer. The importance of pH in this process is shown by the fact that protein synthesis is obtained only in the physiological pH range. Subsequent results by other workers, especially Bergmann's results with papain, have confirmed and extended our observations. We therefore suggested that the lytic and synthetic activity of cathepsin is regulated *in vivo* by the oxygen tension, pH and apparent oxidation-reduction potential in the tissues. Further evidence supporting this view has been obtained by Reiss, who, using electrometric measurements, found that the synthetic function of papain is favored by a positive potential, established by the addition of various oxidizing agents. As to the bearing of these results on the problem of cell proliferation, it is interesting to note that Havard and Kendall, working with tissue cultures in which the oxidation-reduction potential was set at different levels by the addition of redox indicators, found that a low potential, *i.e.*, $E_h - 20$ to -30 m.v. stops all mitosis. Several years ago Warburg reported that exposure of tumor animals to low atmospheric oxygen tensions caused wide-spread tumor necrosis, and Campbell and Cramer observed a considerable decrease in the tumor growth rate.

We have also studied another phase of the problem of the relation of proteins to tumor growth. Classical nutrition experiments have shown that the growth rate of young animals, and therefore tissue proliferation,

does not proceed normally unless the diet contains an adequate amount of so-called essential amino acids. It is of considerable interest, therefore, to ascertain whether or not tumor growth is also inhibited by diets deficient in certain amino acids. The special diets were fed to female mice with small spontaneous mammary cancers. The growth-promoting properties of each diet used were carefully studied on young normal mice. Without going into details it was found that two different diets deficient in lysine caused a striking inhibition in tumor growth. The subsequent addition of lysine to the diet resulted in a prompt increase in the rate of tumor growth.

Experiments with a zein diet, supplemented with lysine, also caused a marked retardation of tumor growth. In this case the addition of tryptophane to the diet did result in a pronounced growth stimulation of the tumors.

Further experiments showed that a diet containing 17 per cent. of dried whole milk powder as the sole source of protein was inadequate for the growth of young mice or for tumor growth. However, when this diet was supplemented with 0.4 to 0.6 per cent. of cystine the young mice grew normally and the growth rate of the tumors was greatly increased. A striking stimulation of tumor proliferation was also obtained when tumor mice on the basal diet received daily subcutaneous injections of glutathione.

Since supplementing the basal diet by methionine has failed consistently to stimulate tumor growth, it would appear that under the conditions used cystine, as such, or in the form of glutathione, is a more powerful stimulating factor than methionine. In this connection reference may be made to the recent important studies of Rose and his coworkers. They find that normal rats lose weight and die if fed on a diet containing an abundant amount of cystine, but no methionine. On the other hand, the animals grow when the diet contains an adequate quantity of methionine but no cystine. Therefore, methionine, but not cystine, is considered an "essential" amino acid. However, if methionine is fed at a level which permits only slow growth the addition of cystine greatly increases the growth rate. If it be permissible to apply to mice the results obtained with rats, it would follow that the basal diet used in our experiments supplied only suboptimal quantities of methionine, and, therefore, the administration of cystine or glutathione stimulated tumor growth. Further experiments on the relation of methionine to tumor growth are in progress.

One important function of the amino acids is to furnish the building stones for the construction of tissue proteins. Evidence is also slowly accumulating which indicates that amino acids possess some other specific biological functions in the proliferation and differentiation of cells and in the synthesis and activities of enzymes. The stimulating action of glutathione on tumor growth may be explained on this basis, since Hammett, and Voegtlin and Chalkley have shown that under certain conditions glutathione stimulates the division of normal cells by accelerating the growth rate of the cell nucleus.

CHEMICAL TREATMENT OF CANCER

The limitations of the surgical and radiation treatment of cancer have encouraged efforts to discover chemical therapeutic agents. For instance, Murphy postulates that tissue growth is controlled by stimulating and inhibiting substances of an unknown chemical nature. It is significant that he and his coworkers found that repeated intraperitoneal injections of extracts derived from placenta or embryo skin into mice with spontaneous mammary cancer arrested tumor growth in about 70 per cent. of the animals, and in 22 per cent. the tumors actually regressed. These changes were accompanied with a marked reduction or absence of mitotic figures in the tumor tissue. More recently they found that a potent inhibiting fraction could be isolated from the mammary tissue of the cow and rabbit in the prelactating or early lactating stage.

During the last few years new interest has been aroused in the apparently selective action of certain bacterial toxins. Workers in the Public Health Service have been engaged in attempts to isolate active fractions from certain bacterial filtrates. Such fractions isolated from filtrates of *B. prodigiosus* grown on a synthetic medium, when injected into mice with rapidly growing transplanted sarcomas, cause severe hemorrhages in the tumors and many of the growths regress. This action is apparently due to rupture of the fragile, newly formed blood capillaries in rapidly growing tumors.

The old gout remedy colchicine, a phenanthrene derivative, is known to arrest mitosis, and suggestive results have been obtained, indicating that the growth of certain mouse tumors can be inhibited by this drug.

Quite recently Strong reported extensive liquefaction and complete regression of spontaneous mammary cancer in mice following oral treatment with heptylaldehyd.

Experiments are also in progress in several laboratories designed to discover artificial radioactive substances with a selective action on tumor tissue. Success in these efforts, I believe, will largely depend on the selective distribution of the substances in malignant tissue. It is possible that radioactive iodine may perhaps be useful in the treatment of neoplasia of the thyroid.

Hammett and Reimann have observed an inhibiting effect of cystine disulfoxide on the growth of mammary cancer in mice. We have carried out well-controlled experiments with a series of synthetic aromatic sulfur

compounds and find that some of these have a definite inhibiting action on the growth rate of spontaneous mammary cancer in mice.

This survey of the experimental chemical treatment of tumors is merely intended to demonstrate that at least some suggestive results have been secured in this field. In view of the quite unexpected recent development of the chemotherapy of bacterial diseases it may not be over-optimistic to look forward to the time when similar results can be achieved in the chemical treatment of neoplasia.

In conclusion I hope that I have shown that encouraging progress has been made in the study of certain chemical aspects of cancer. There is every reason for looking forward confidently to the rapid accumulation of new knowledge, which will be helpful in the gradual solution of this important and baffling problem. It is most gratifying that the establishment of several well-endowed cancer research foundations and the recent creation of the National Cancer Institute have furnished the means for a concerted scientific attack on this devastating disease.

OBITUARY

DR. FRED BAKER

WITH the death of Dr. Baker, of San Diego, Calif., on May 16, 1938, a life of a very exceptional combination of valuable human qualities came to an end. Medical practice, specialized on eye, ear, nose and throat, was his sole means of livelihood and with his wife, also a physician, yielded a good family income.

Born at Norwalk, Ohio, on January 29, 1854, from early boyhood to the very end Baker's love of natural history was one of his foremost traits. Even his undergraduate course at Cornell was interrupted by extensive trips in Europe and Latin America, through all of which his broad naturalist proclivities were strongly to the fore.

Following graduation in medicine at the University of Michigan by him and his soon-to-be wife during the early eighties, after several thrilling experiences they found themselves (1888) in San Diego where, known to the community as Dr. Fred and Dr. Charlotte, their notable careers began at once. Being here chiefly concerned with Dr. Fred as a scientist, about him as a physician nothing need be said beyond reference to the extent to which he was recognized officially and otherwise by the profession of his city, county and state.

His contributions to natural knowledge as a researcher were limited to the mollusca, mainly as a conchologist. In this field he is widely known for his addition to knowledge of the marine fauna of Pacific North America; but still more probably to that of Brazil. His large paper on the last contained not only the descriptions of many new species, but important information on distribution and other ecological matters owing to his having done most of the collecting himself.

Up to near the end he was occupied, in collaboration with J. R. Le B. Tomlin, of the British Museum, on an extensive paper on Brazilian mollusca.

But a full account of his publications in this and other fields would be far from an adequate exhibit of his contributions to science. As a collector (and this for him meant an explorer) his record is surprising. Thus from his own biographical notes: "On all their travels the Bakers have collected extensively specimens in conchology, botany and ichthyology, which have been given to the National Museum at Washington, the California Academy of Sciences in San Francisco, the Academy of Natural Sciences in Philadelphia, the University of California at Berkeley, and its Scripps Institution of Oceanography at La Jolla, and finally to the San Diego Museum of Natural History goes his own great working collection of shells."

His activities in connection with the Society of Natural History of San Diego were so extended in time and so efficient that it is hardly possible to speak of the institute apart from him.

But of all his efforts in behalf of institutionalized science, he regarded his part in the founding and operating of what is now the Institution of Oceanography at La Jolla, a branch of the University of California, as the most important. And surely no one who has had a hand in that enterprise can hesitate for a moment to acknowledge his service in that connection.

Finally a few sentences on his ideas and acts in the realm of civics. His years of service on the city council and the board of education—part of the time as president of both—and on the board of the then State Normal School at San Diego must suffice except for this one remark: Although never, so far as I recall, did I hear him say anything of the sort I am sure that in all these varied relations and activities he maintained much of the scientific attitude especially as this appertains to natural history. Whether as a physician dealing with defective vision of a patient; or as a member of boards dealing with the affairs of the Society of Natural History, or of the Institution of Marine Biology; or as a member of the city council dealing with the water problem; or as a member of the board of education dealing with the question of the presidency of the board, I am sure his youthful in-