The meeting of the Council was held at the New Ebbitt Hotel, on the evening of Sunday, April 30, 1922, at eight-thirty o'clock.

The following members were present: Dr. James B. Murphy, president; Dr. Willy Meyer, vice-president; Dr. Wm. H. Woglom, secretary and treasurer; Dr. H. Gideon Wells. Absent: Dr. Francis C. Wood, Dr. Robert B. Greenough, and Dr. James Ewing.

The report of the treasurer for the year showed a balance on hand of $466.41. The treasurer also reported that the gifts made to the JOURNAL during the past few years by private individuals or various funds had not been entirely expended when the JOURNAL was taken over by the Crocker Fund and that $266.71 of such moneys still remained in the treasury. He asked the members of the Council whether this money should be divided into aliquot parts and returned to the various donors, or should be kept in the treasury. It was decided that it would be justifiable to allow this money to remain the property of the Association, Dr. Wells expressing his opinion that Dr. Ormsby, for example, would rather have his gift used by the Association. It was pointed out, furthermore, that in the case of the contribution from the members of the staff of the Gratwick Laboratory, the amount returned to each would be so small as to be practically negligible. The treasurer was, therefore, instructed to retain this money in the treasury of the Association, and if necessary to expend it for general expenses in connection with meetings, etc.

The name of the following applicant came before the Council for election to the Association:

Dr. Isidore Kross, 20 West 50th Street, New York

Dr. Kross was elected an active member.

The resignations of the following members were accepted:

Dr. G. R. Minot Dr. J. A. P. Millet

The secretary was instructed to write to Dr. J. P. Hoguet and Dr. Hugh H. Young, who also had sent in their resignations, asking them to reconsider their determination and pointing out that the Association at the present time, more than ever, needed their support.
Dr. Frederick Prime, New York, was elected to the Council to succeed Dr. Francis C. Wood, automatically retired by the time limit. The following officers were elected for the ensuing year: Dr. Willy Meyer, president; Dr. William Duane, vice-president, Dr. Wm. H. Woglom, secretary and treasurer (re-elected).

The present members of the Council, with the years of their retirement, are:

- Dr. James B. Murphy, 1923
- Dr. Wm. H. Woglom, 1924
- Dr. Robert B. Greenough, 1925
- Dr. Willy Meyer, 1926
- Dr. James Ewing, 1927
- Dr. H. Gideon Wells, 1928
- Dr. Frederick Prime, 1929

The present Editorial Board was continued in office:

- Editor, Dr. Woglom
- Associate Editor, Dr. Prime
- Dr. Bloodgood
- Dr. Wells
- Dr. Loeb
- Dr. Ewing
- Dr. Tyzzer

It was suggested that the Journal might be made more popular by publishing from time to time reviews of various phases of the cancer problem. The secretary was instructed to write to each member of the Editorial Board to ask for opinions on this proposal.

2. DEMONSTRATION OF GONGYLONEMA CARCINOMA

Dr. Julius Rosenstirn (New York):

SUMMARY

Dr. Rosenstirn stated that in June and July of 1920 he worked for six weeks in the laboratory of the Pathological Institute of Copenhagen, where he made himself familiar with the methods of cockroach experimentation of Dr. Fibiger, who furnished him with a host of cockroaches not infested, with five of the stock of his rats, and an equal number of infested mice, all of which were brought to the Crocker Institute. The life cycle of these nematodes, the intermediate host of which is the cockroach, was described. Either artificially or spontaneously infested mice or rats shed with their feces the ova containing the embryos of the nematode at first classified as spiroptera by Fibiger and Ditlevsen. This classification was later changed by Ransom, who regarded this nematode as belonging to the family Gongylonema, and the correction has been adopted by Fibiger and his collaborator, who since term it Gongylonema neoplastica. These ova-carrying feces of the infected animals are fed to the cockroaches. Of the three kinds of cockroaches—the Periplaneta americana, Periplaneta orientalis, and the germanica—only the first two, the americana and the orientalis, can be regarded as serviceable for these experiments. The germanica is entirely inadequate, mainly on account of its smallness, and the best, the americana,
seems to be extremely hard to obtain. The experiments under dis-

cussion have been carried out exclusively with the orientalis, with which

great difficulties were experienced until lately, in consequence of fol-

lowing too closely Fibiger's suggestions. He advised that they be kept

at a temperature of 30°C., but at this temperature the cockroaches
died. When they were kept at 17° to 20° they did well. The eggs are

eaten with the feces by the cockroaches; the embryos are freed in the

intestine, and migrate gradually, developing into the larval stage,

into the muscular system, where they are encysted somewhat like the

Trichinae. The muscular parts of the infested cockroaches are fed to

the rats, and the larvae lodge in the mucous membrane of the stomach,

where they mature to the adult form of the Gongylomena. At times

some of the larvae remain in the tongue and wander from the mucous

membrane into the lingual musculature, where they produce the same

pathological changes as in the stomach. In a certain percentage of

cases carcinoma of the stomach, or rather of the so-called pro-stomach,

the cardiac portion of that organ, is caused by the presence of the

parasites.

DISCUSSION

Dr. H. Gideon Wells (Chicago): I should like to ask if in Fibiger's

experiments there was any instance of carcinoma of the glandular por-

tion of the stomach. It is rather remarkable that in those animals

with a rumen, it is not uncommon to find squamous cell carcinoma of the

rumen, but never of the glands of the fundus. In carcinoma of the

stomach in mice, there are 9 or 10 cases, reported and unreported, in

which the carcinoma has always been in the cardia, except in 1 case of

a carcinoma of the glandular type. I take it there is some factor of

importance here, since carcinoma of the glandular type is the variety

seen in man; yet it is exceedingly rare in all the lower animals.

Dr. Erwin Smith (Washington): On the roots of plants destructive

tumors due to nematodes (Heterodera radicicola) have been known

to botanists for a long time. In these cases, as in the case of the nem-

atode infections obtained by Fibiger in rats, the entire body of the worm

is buried in the tumor so that all the excretions of the worm pass into

the surrounding host tissues. In this connection it is interesting to

know that in Florida there is a nematode on the roots of the orange

tree which does not produce any tumors, although Dr. Cobb states that

it is closely related to the tumor-producing Heterodera. In this case

only the head of the worm is inserted into the tissues, which are sucked

dry and killed. The rest of the worm, including the excretory organs,
is outside of the root in the soil, and I believe that this is the reason that

in the one case tumors are produced, and in the other not produced.

Giant cells are very common in the nematode tumors of plants. Often

they contain a great many nuclei, and I have seen as many as fifty in a

cell. These giant cells, which appear very early in the life of the
tumor (earlier than the sixth day) are, so far as I have observed, always close to the head of the worm, which probably feeds upon their contents. In remoter parts of the tumor there is an hyperplasia. The whole tumor is soft and very perishable.

Dr. E. T. Bell (Minneapolis): I want to call attention to a certain resemblance of this growth to the well known coccidiosis in the liver of rabbits. This is a very common condition; the coccidia grow in the intestines and in the hepatic ducts. There develops an extreme hyperplasia of the epithelium with enormously dilated ducts,—a condition which we might call an adenomatous growth, but never, so far as I know, does malignancy develop. The organisms are embedded in the epithelial cells.

Dr. Rosenstirn: In reply to Dr. Wells, I may say that the cancers develop exclusively in the cardiac portion of the stomach, the so-called pro-stomach, never in the pyloric part, which in man so frequently is the seat of carcinoma. Whether this is due to the different types of glandular structure or of the epithelium in these parts, I do not know, but the fact remains that neither Fibiger nor myself have ever observed these pathological changes outside of the pro-stomach. Concerning the changes produced by nematodes entirely buried in plants, and their absence in the Florida plants, in which only the head lodges and the secretions of the nematodes are poured into the earth, I can not now determine if there is any justification in arguing from the action of these parasites on plants to the action of others on the rat stomach. The secretion of the nematode into the tissues may be an auxiliary factor in producing the hyperplastic and cancerous neoformations. This question, although discussed, has been left open by Fibiger, and its decision appears to offer nearly insurmountable difficulties.

I do not quite agree with Dr. Bell’s view of an existing analogy in the growth we meet in coccidiosis and the tissue changes produced by the Gongylonema. The new-formed coccidiosis growth is strictly a granulation tissue undergoing a degenerative process later, whilst here we have an epithelial growth developing into typical cancerous tissue in its final development. Nor does the parasite of coccidiosis in its adult form attain a liberated free motility; it remains encysted.

3. APPOSITIONAL GROWTH IN CROWN-GALL TUMORS AND IN CANCERS

Dr. Erwin Smith (Washington):

SUMMARY

Numerous lantern slides were shown indicating clearly that the growth of crown-gall is chiefly peripheral, as in cancer, and that the lobes of the tumor enlarge by the conversion of a narrow ring of normal tissue into tumor tissue. The full paper has been published in this JOURNAL.
In closing, Dr. Smith called attention to the fact that there is no agreement among oncologists as to appositional growth in cancer. Virchow and practically all oncologists down to Ribbert maintained that primary tumors grow by conversion of surrounding tissues of the same type into tumor cells, i.e., by apposition. Ribbert and his school, on the contrary, denied this *in toto*. Leaving Virchow and his colleagues out of consideration because their work is now old, modern workers as well qualified to judge as Ribbert, Borst, and Borrmann, i.e., such men as Hauser, Hansemann, Ziegler, Menetrier, and others, have strenuously maintained that growth by apposition does occur in primary cancers and some of them have offered instructive figures in proof of their contention. The speaker concluded by saying that the question must be regarded as still unsettled. If growth by apposition does occur in cancer, then, in the light of what he has just shown, it points strongly toward the parasitic origin of cancer. If, on the contrary, it does not occur, parasitism is probably not the cause of the disease.

**DISCUSSION**

*Dr. Isaac Levin* (New York): About sixty-five years ago, Virchow, in his book, began the study of cellular pathology with plant cells. He then compared animal with vegetable tumors, and urged pathologists to become acquainted with botanical material and to compare plant and animal tumors, and other pathological conditions. However, we pathologists have forgotten this advice, and when I began a few years ago to be interested in the study of plant neoplasia it was not Virchow's opinion, but a perusal and study of the splendid work of Dr. Smith, that made me take up the problem. In the course of six years' work I have occasionally disagreed with one detail or another of Dr. Smith's findings, but the life of a scientist would be very monotonous if he had no arguments with his fellow-scientists. I am sure that Dr. Smith has always taken my arguments in the right spirit and as a stimulant to further research. But outside of that, I wish to express my appreciation, and I am sure that I voice the sentiment of every man in this country or elsewhere who is doing cancer research, when I express our realization of the splendid contributions Dr. Smith has made to cancer research, and I wish to congratulate him here on his years of very valuable labor.

*Dr. Michael Levine* (New York): I should like to ask how frequently do nuclear divisions occur in the crown-gall. I have been comparing them with epitheliomas, and I believe that mitoses are not so common as they are there. Perhaps in Washington crown galls can be grown under better conditions than we have in New York.

*Dr. Smith*: In reply to Dr. Levine's question, I would say that there are just as many mitoses in crown-gall as there are in cancer, but to
see them the material must be collected and fixed in the middle of the night, the best period being from midnight to about four o'clock in the morning. The tumors which furnished the sections I have shown today were collected in the early afternoon and there is less than one mitosis per field of the microscope. Had they been collected in the middle of the night there would have been a number of mitoses in each field. There are some amitotic divisions of the nucleus in crown-gall, but the bulk of the divisions is by mitosis, the same as in cancer. I have found cells in crown-gall with two nuclei, and more rarely with four, and once as many as seven nuclear fragments, but in general these multinucleated cells are exceptional, and in these particular tobacco tumors they occurred almost entirely in the transition tissue on the margin of the tumors.

4. ATTEMPTS AT THE PRODUCTION OF CANCER BY RADIIIM

Dr. W. S. Lazarus-Barlow (London):

SUMMARY

This paper, illustrated by lantern slides and microscopical sections, described attempts at the production of carcinoma in animals by means of radium. Starting from his researches (1) on a stimulative action upon the division of ova of Ascaris megalcephala and upon muscular activity (frog) exerted by the rays of radium; (2) on the presence of radium in cancerous tissue; and (3) on the presence of radium in certain gallstones, the speaker discussed the appearances produced by the introduction of radium beneath the skin of rats and of radium-containing gallstones into the gall bladders of rabbits. He submitted that the changes produced are histologically indistinguishable from early carcinoma, being of the squamous cell type in the rat's skin and of the columnar cell type in the rabbits' gall bladder. In the case of one rabbit a true metastasis occurred. In the case of rats the fact that removal of the radium (whether through ulceration or by operation) was followed by regression of the early appearances suggestive of carcinoma, led him to endeavor to break down artificially the natural immunity against cancer which rats seem to possess. This was done by (a) feeding with potassium metaphosphite; (b) by repeated, moderately severe irradiation with X-rays over a period of eight to ten weeks; or (c) by a combination of the two agents. When radium was introduced intraperitoneally into rats thus prepared, a larger percentage of cases presenting histological criteria suggestive of malignant disease occurred. The author regarded the experiments as still inconclusive, in the sense that no rat presented a clinical picture recalling malignant disease in man. The lesions were always small in the immediate neighborhood of the radium tube, however closely they might resemble carcinomatous material histologically. He felt that if only it were possible to break down this natural immunity in the rat and produce a
definite carcinoma at will, a great step would have been taken in our knowledge of the disease. Experiments are still proceeding on similar lines at the Middlesex Hospital, and in addition tar is being used as the exciting agent.

The speaker also referred briefly to a projection apparatus, capable of being used in diffuse daylight and operated by the lecturer himself in class demonstrations. The essential points are, that a gas-filled incandescent lamp of 1500 c.p. replaces the arc, and that the image is thrown upon a ground glass screen and viewed by the students by transmission.

5. PRIMARY SPONTANEOUS TUMORS IN THE KIDNEY AND ADRENAL OF MICE: STUDIES ON THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS TUMORS IN MICE. SEVENTEENTH REPORT

Miss Maud Slye, Miss Harriet F. Holmes, and Dr. H. Gideon Wells (Chicago): Presented by Dr. H. Gideon Wells:

SUMMARY

Primary tumors of the kidney occur not infrequently throughout the animal kingdom, and, in general, seem to exhibit the same variations and peculiarities seen in human renal tumors.

The authors reviewed the literature on the occurrence of renal tumors in animals. All told, they can find records of but 6 cases hitherto reported in mice, all being of epithelial character. In rats, both wild and tame, renal tumors are somewhat more frequent; of 156 reported cases of rat tumors, 27 were in the kidney, all epithelial despite the fact that the other tumors of rats are often sarcomatous. Swine seem to be the only domestic animals in which renal tumors are common, the Wilms type of mixed tumor being most often seen. Renal tumors are not rare in horses, but they are very infrequent in cattle or sheep. No reports of adrenal tumors in mice have been found.

In a series of 33,000 autopsies on mice of the Slye stock, dying natural deaths at all ages, but as far as possible living out their natural span of life, there have been observed the following cases of true primary neoplasm arising from renal or adrenal tissues: (1) From the kidney, 16 tumors, classified as follows: 1 carcinoma, 3 adenomas 1 hypernephroma, 7 sarcomas, 3 mesotheliomas, and 1 sarcoma of the renal pelvis. (2) From the adrenal, 4 tumors, as follows: 1 cortical adenoma from a misplaced inter-renal adrenal rest, 3 mesothelial tumors. (3) Five cases of tumors of the mesothelial structure characteristic of urogenital anlage neoplasms, but the exact origin of which could not be determined because of their widespread growth at the time of death. As these 25 tumors occurred in 33,000 mice presenting not far from 5000 other tumors, they are evidently uncommon tumors of mice, at least in this particular stock.
It will be noted that in this series there has been no instance of a mixed renal tumor of the Wilms type, which is so common a type of renal tumor in man and apparently also in swine. Although inflammatory conditions are very prevalent in the kidneys of mice, epithelial tumors are rare, and especially to be noted is the absence of even a single case of typical malignant hypernephroma, although one benign growth of this type was found. Also no epithelial tumors of the renal pelvis were found, although there was 1 case of sarcoma that seemed to take its origin in the pelvis.

Several instances of malignant retroperitoneal tumors have been observed, mostly of sarcomatous structure, which usually invade the kidney. These have not been included in this series, except 2 cases in which the structure resembled that of the mesotheliomas, suggesting that the tumor had its origin in misplaced rests of the urogenital anlage.

Secondary tumors have never been found in the adrenals, and but rarely in the kidneys. Although this series includes at least 3000 cases of mammary gland carcinoma, often with widespread metastases in the lungs, we have never seen a secondary growth in the kidney. The only secondary carcinomas of the kidney as yet observed are four cases in which the primary carcinoma was in the lung, thus establishing the true neoplastic nature of these lung growths. In but 2 cases have hematogenous metastatic sarcomas been seen in the kidney, if we exclude the numerous cases of invasion of the kidney by direct extension from pararenal growths.

As to sex, taking the entire group of renal and adrenal tumors, there was an equal number in males and in females, agreeing with the observation made with other tumors in mice that, in tumors not peculiar to the sex glands there is usually little difference in incidence in the two sexes.

Differing from the tumors previously studied, coincidence of other tumors with the renal and adrenal tumors is uncommon. One mouse had a spindle cell sarcoma of the thigh. One had a small, benign papillary adenoma of the lung. Only 2 mice had a mammary gland carcinoma, and one of these (21663) was a remarkable case, for this animal, although but one month and eighteen days old, had two independent mammary gland carcinomas, osteosarcomas in the spinal column and in a rib, and a mesotheliomatous type of growth involving both kidneys. Except for this unique case there have been practically no instances of malignant tumors in mice less than four months of age, and few under six months. Most of the renal sarcomas occurred between the ages of seven months and one year, which is somewhat earlier than the usual time of appearance of epithelial growths; this, of course, corresponds to experience with human neoplasms.

The epithelial renal-adrenal tumors furnished no illustration of metastasis, but in 3 cases of sarcomatous or mesotheliomatous growths there was noted involvement of the adjacent lymph nodes, in 2 there were pulmonary, in 2 hepatic, and in 1 splenic metastasis, and in 1 case there were numerous peritoneal growths. The mesothelial type of growth
produced the most extensive metastasis and the most widespread infiltration of the body wall.

**DISCUSSION**

*Dr. Bell:* I once studied a series of 100 malignant tumors of the adult kidney. They are very different from those of the child. In that series there were 2 fibrosarcomas in which collagenous fibrils could be identified, so that there was no doubt of their being sarcomas. All the others ranged from a definite adenocarcinoma down to a round cell sarcoma, and every possible transition between carcinoma and sarcoma was observed. In some of the tumors there were definite tubules in the primary renal tumor, and the metastases had the appearance of a round cell sarcoma. These variations are clear if one keeps in mind the origin of the kidney from the metanephrogenous tissue. For that reason it seems to me that we should not make any distinction between these different types of tumors. The objection to the term mesothelioma is that it is a comprehensive term for all of the tumors of the ovaries, testes, and kidneys, and cannot be differentiated from the sarcoma or carcinoma by structural peculiarities. I should like to ask Dr. Wells if he has any objections to the term nephroma.

*Dr. Levin:* If one could have an experimental laboratory with 10,000 human beings and keep on inoculating the tumors from one to another, I am sure that human tumors would also be found inoculable.

*Dr. Wells:* I prefer the term "mesothelioma" for the very reason Dr. Bell disapproves of it. It is a general term, and in many of our cases I cannot tell whether the mass arises in the adrenal or in the kidney, but it evidently arises from the mesoblastic embryonal tissues and so, therefore, I use a general term. I do not like the tendency to adopt the term "nephroma," any more than I like "thymoma," and similar terms. We would have equally to use "hepatoma," "cerebroma," and so on, and it would make an absurd nomenclature. The term mesothelioma does mean tumors arising from a mesoblastic origin and producing epithelial structures, showing every possible transition between one form and another.

6. **ON THE RÔLE PLAYED BY CARBON DIOXIDE IN CONTROLLING CELL PROLIFERATION**

*Dr. G. H. A. Clowes and Homer W. Smith* (Indianapolis).

7. **THE ACTION OF RADIUM EMANATION ON NEOPLASIAS IN PLANTS**

*Drs. Isaac Levin and Michael Levine* (New York):

In previous communications the writers have shown that plant tumors present an ideal material for the study of the direct action of x-rays and radium on the tumor cell. The so-called "buried emana-
"Method of radium therapy is constantly becoming of greater importance in the treatment of cancer in the human patient. It consists in placing a minute glass capillary filled with radium emanation into the tumor. Both the softest beta as well as the hardest gamma radiations act on the tumor tissue surrounding the capillary, while the alpha rays are absorbed by the glass.

The present investigation consists in the application of this method to neoplasias in plants in order to ascertain the mechanism of the direct action of radium on the tumor cell. Young growing and adult tissues were used for purposes of comparison, while crown-gall and club root tissues were the main material. Capillary tubules 3 mm. long and 0.26 mm. in diameter, containing from 0.5 to 3 mc. of radium emanation were inserted into growing points of tobacco, adult roots of the turnip, crown-gall tissue of geraniums, and young club root tissue of the turnip. Empty tubules equal in size to those containing the emanations were inserted in identical tissues as controls. The insertion of the radium emanation was done at various intervals after the beginning of the formation of the crown-gall or club root. The development of the radiated tumors was noted and the radiated neoplastic tissues were removed for microscopical examination from one day to several weeks after the insertion of the capillary.

The analysis of the results of these studies shows the following: the insertion of the radium emanation is followed by a general inhibition of the development of the crown-gall or club root, which tallies well with the results obtained by the writers previously by x-raying the crown-gall. Consequently the hard gamma ray fraction of the radium emanation capillary tubes produces the same effect on the tumor as the x-rays or the filtered gamma rays of radium applied at a distance from the tumor.

In the tissues in the immediate vicinity of the tubes deeper changes in the tumor cells were noted. Section of this region shows the collapse of cell walls radially to the needle, forming a cushion of cellulose. The cells immediately behind this cushion are devoid of cytoplasm. Occasionally one finds a nucleus in process of disintegration. In cells further back of this area one finds unchanged nuclei.

In club root tissue the degenerated cells immediately adjoining the so-called cellulose cushion do not seem to contain the Plasmodiophora brassicae, while the parasite is present in the cells at a further distance from the capillary. This apparent action of radium on the parasite as well as the more minute study of the intracellular changes caused by the irradiation is a subject of further study by the writers and will be reported later. It is rather significant that the cellulose membrane of the plant cell seems to play a similar role in plants in walling off the necrotic area about the emanation tubes and filtering off the soft radiations as the lymphoid tissue stroma does in animal tumors.
8. DEFENSIVE FACTORS AGAINST CANCER

Dr. William Carpenter MacCarty (Rochester):

SUMMARY

Dr. MacCarty called attention to the fact that in the study of post-operative histories and results, one is often surprised to find the patient living nine or ten years after extirpation, though complete involvement of the lymph-nodes had been found at operation. This is especially striking when one compares these cases with others having small cancers and no glandular involvement, who have died six months or two years after operation. The present study was undertaken to determine, if possible, whether there were any factors which might have some influence on this increased longevity. In connection with this the following conditions are considered: lymphocytic infiltration, fibrosis, hyalinization, and the degree of differentiation of the cells of the cancer itself.

The records of 99 gastric cancers, 92 breast cancers, and 102 cancers of the rectum were studied. All the operations were done in the same way by a group of surgeons who had received the same training. All the patients died of recurrent or metastatic cancer.

A study of the relative frequency of the factors just mentioned shows that differentiation occurs in 65 per cent of the stomach cases, 8.6 per cent of the breast cases, and in 86 per cent of the rectal cases. There is, therefore, a great variation in the frequency of occurrence of these different factors in different organs of the body. Fibrosis in the stomach is a rather rare condition. The same is true of hyalinization, but in the breast and in the rectum this factor occurs quite frequently.

Tables were presented to show the combination of the different factors, and the variation in the different organs. A comparison was made of the average length of post-operative life when the factors were present and when they were absent. For example, in the breast with differentiation the average length of life is 3.65 years; without differentiation 2.35 years. Whenever the factors are present, the average length of life is increased over when the factors are absent.

As a result of this study, it appears that there is a constant increased longevity when these factors are present, either alone, or in the various combinations, and that the greatest increase is associated with differentiation and hyalinization, in combination or alone. Since these figures were collected, a study of epithelioma of the lip and of the skin and other portions of the body has shown the same results. The explanation is left open, but it is known that the more differentiated a cell, the less power of reproduction it has, except the highly specialized sex cells, and also that hyaline tissue is a very dense tissue and that penetrability is in proportion to the density.

9. PRELIMINARY REPORT ON TUMOR GROWTH FOLLOWING INJECTION OF RADIATED TUMOR EMULSION

Dr. M. J. Sittenfield (New York).
10. Biological Evidence for the Inheritability of Cancer in Man

Miss Maud Slye (Chicago):

Abstract

The biologic problem of the nature and inheritability of spontaneous cancer has been under study in this laboratory for the past twelve years, during which time the results consistently obtained have demonstrated the fact that cancer is inheritable. Among the many thousand mice bred in this laboratory in the study of cancer heredity, there has been no case that does not agree with this conclusion—no appearance of spontaneous cancer in a non-cancer strain, nor any line into which cancer has been bred where it has not appeared in exact accordance with the known laws of heredity. The inheritance behavior of cancer has consistently been that of a simple Mendelian recessive.

It is therefore a demonstrated fact that cancer is inheritable in mice, and this fact is now pretty generally accepted.

The profound and biologic aspect of this demonstration of the inheritability of cancer, however, has for the most part failed to be grasped by the pathological and medical world, and the object of this paper, therefore, is to emphasize that phase of the study, and to make clear the exact application of this demonstration to the problem of the inheritability of cancer in man.

Every instance of organic behavior is based upon biological law. Many of these laws are as yet not even foreshadowed. In the case of the law of heredity, however, which is the most fundamental and most potent of all biologic laws, we have the fundamental facts. But although we have these facts, we continue in actual opinion and practice for the most part entirely to ignore them.

If we give heredity its full biologic definition, we must define it as follows: Heredity is the force which makes and holds together the genus and the species. It determines what form, what characteristics and what activities, in the most complete sense of the words, every genus, every species, and every individual shall have. It determines the beginning of every organism as a single cell, each (after the unicellular forms) in its development undergoing cell division and differentiation, and each recapitulating in hurried fashion the history of organic evolution which has preceded it. This is true of man as it is of every other organism which antedated him in the process of evolution. Each organism has been made from organisms which preceded it, and which set aside the germ plasm, with all its potentialities, from which the offspring develops.

Out of this fact grows the biologic law of heredity which underlies all life: That which goes into the germ plasm must come out in the offspring. This applies to every living organism from unicellular plants to man. Each individual develops out of germ plasm laid down with all its potentialities by individuals which preceded him; in every item made out of material furnished by his ancestors.
Man, then, developing from germ plasm laid down by his ancestors, inherits the same type and behavior of tissues shown by his ancestors.

The method of heredity was worked out by Mendel with green peas. Later and following him Cuenot and others worked it out with mice, and found the method of heredity identical in mice with that in peas.

In the scheme of evolution mice are far removed from peas, but closely related to man, who also belongs to the mammalian group. The structures of mice are like those of man, their tissues behave like those of man because they were derived from a common ancestry. This is the functioning of the law of heredity which transmits each type of protoplasmic behavior down the full line of evolution.

This is the heart of the theory of evolution and without it nothing remains of that theory, which is no longer questionable, but a working tool in science from astronomy to psychology.

What goes into the germ plasm comes out in the offspring. Similar tissues must behave in similar fashion if there is to be such a thing as species or race. Without this fundamental fact the organic world would be chaos. Similar tissues derived from a common ancestry must behave in a similar way.

The mouse tumors under study in this laboratory are spontaneous neoplasms arising in the natural life of the animal without artificial interference of any sort except that of selective breeding, exactly as man's spontaneous tumors arise. They arise in the same tissues and in the same organs as the tumors of man; they follow the same clinical course; they cause death in the same ways. Under the microscope they present the same appearance as similar tumors in similar organs in man. They are the same biologic entity as similar tumors in man. And consequently if we do not discard the entire theory of evolution, we must admit that they behave in the same way in the matter of heredity as in all other matters.

Moreover, accurate human statistical evidence when it is correctly and biologically read, also demonstrates the inheritability of cancer in man.

As already stated, cancer behaves like a Mendelian recessive, like albinism and spotting and the whirling habit of the Japanese waltzer. If only recessives are bred, the dominant will be lost. If this type of breeding were exclusively pursued, the non-cancer tendency would be lost, just as the pigment-making tendency would be lost if only albinos were bred. Recessives cannot transmit the dominant.

The suggestion is also made that in order to avoid artifacts in our animal experimentation, biologically analyzed stocks must be used.

RECAPITULATION

1. Cancer and non-cancer segregate out and are transmitted as such.
2. They are therefore unit characters.
3. A specificity of tissue type from organ to organ segregates out and is transmitted as such.
4. It is therefore a unit character.
5. Since these things are unit characters, it is possible to manipulate them by selective breeding and thereby to implant them indelibly in any species, or to eliminate them permanently and completely from any species.
6. Cancer and non-cancer behave like the absence and presence, respectively, of a mechanism fitted to control proliferation and differentiation in regenerative processes, and an animal either has it, or lacks it, no matter to what species he may belong.
7. There is therefore a ready and certain genetic method of escape from cancer for the individual and the race.
8. The demonstration of the inheritability of cancer in mice is a demonstration of the inheritability of cancer in man and in all other species which show it, if we are to maintain the theory of evolution.
9. The study of cancer behavior, which has demonstrated itself to be fundamentally a biologic problem, points the way to the understanding of all pathologic conditions.
10. And, therefore, when biology underlies all our pathology and bacteriology, all our physiology and therapy, there will no longer be these monstrous diseases, but only the slow and natural death, which is the fatigue and diminution and final cessation of the organ and the organism.

OF GENERAL BIOLOGIC IMPORT

1. From the procedure of analyzing stock into its unit characters in order to learn how to manipulate cancer, there has emerged the fundamental law of heredity—what goes into the germ plasm comes out in the offspring.
2. Every organism is a complex of unit characters and cannot be correctly interpreted or manipulated in experiments with a certain outcome, until it has been analyzed into its unit characters.
3. The unit character as the biologic ultimate, like the ion in chemistry, is the explanation of all biologic and hence of all pathologic syntheses. And all such syntheses can be understood and manipulated, only when they have been analyzed into unit characters.

DISCUSSION

Dr. Smith: I have listened to Miss Slye’s paper with the greatest interest, and I am willing to concede in the matter of heredity that one may reason from mice to men. I believe she has established clearly that if we could select our ancestors we could all escape cancer. In other words, if we could breed men as we breed mice, a race of men could be developed immune to cancer. But there are two factors constantly operative on all living things, only one of which has been stressed by Miss Slye. These two factors are heredity and environment. She has shown clearly that by breeding mice from cancerous parents she has obtained a race 100 per cent cancerous, and by elimina-
tive breeding a race 100 per cent free. I believe the same thing could be done with crown-gall or with tuberculosis; and yet that would not prove that the two diseases I have mentioned are due to heredity. So I believe that in all probability there is a cancer parasite able to act on certain strains of her mice, and not able to act on others. If it occurs at all, it is probably some organism transmitted from cage to cage and mouse to mouse by some common ectoparasite. I can think of whole families of persons who died of tuberculosis—father, mother, and half a dozen children—and there the tendency was very strong, but the tendency itself was not the cause of the disease.

In the case of crown-gall in very susceptible species, I would not stress the necessity of pure strains as Miss Slye is inclined to do; for, taking the plants as they run, in these species I can get 100 per cent of takes in my inoculations. I have now about 50 inoculated Pelargoniums, every one of which has taken the disease, but in other plants, like the rose, there is great variation in susceptibility.

Dr. Sturges: May I ask whether, in the case of chimneysweeps' cancer, where environment plays such a very large part, there is a question of heredity underlying the cancer? And does this apply to the experimental cancers of rabbits' ears?

Dr. Rosenstirn: If the laws of cancer heredity in mice are equally valid for man, then, in the human being, where both parents have cancer, would you expect an unbroken series of cancer in their direct offspring, that is, in those who lived long enough to develop the disease?

Miss Slye: I must object to Dr. Smith's using as an argument the assumption (which must remain merely an assumption until it has been demonstrated experimentally) that you can breed out either tuberculosis or artificially induced crown-gall. In the meantime the fact that spontaneous cancer is hereditary is experimentally demonstrated.

I have not in this paper made any mention of the parasite theory of the origin of cancer, nor is there occasion or time to do so in the discussion. Moreover it is the strong, and not the weak, individuals that develop cancer both in mice and in the human species. Herein cancer is conspicuously different from known infections, as it is conspicuously different from them in many other ways.

In reply to Dr. Sturges: The stocks both of rabbits and mice which have been used in the production of "coal tar cancers" were not in any case tested as to their tendency to spontaneous cancer. It is therefore impossible to say whether or not they would have produced spontaneous tumors. The chimneysweep and x-ray cancers of man seem to me to be closely related to these experimentally produced cancers in animals. This subject will be discussed in another paper, which I was unable to prepare for this meeting.

In reply to Dr. Rosenstirn: In the human species where both parents have spontaneous cancer, I would certainly expect cancer in the
offspring who lived to cancer age, and who were subjected to the type of chronic irritation fitted to occasion cancer of the type and in the organ predisposed by heredity to such cancer. The paper which I have just presented was intended to answer exactly the question which Dr. Rosenstirn has asked.