Meetings

International Cancer Congress

Cancer is a relentless enemy of mankind, yet its story is filled with human triumphs as well as suffering. This thought was never too far out of sight during the recent meeting of nearly 2500 cancer research workers from 64 countries, who convened in London from 6 to 12 July for the 7th International Cancer Congress. During the many sessions, symposia, and discussions, the current status of the cancer problem in 1958 gradually evolved in all its fascinating intricacies, uncertainties, and successes.

Theory of Carcinogenesis

In a congress plenary session on carcinogenesis, Sir M. Burnet (Melbourne, Australia) outlined his simple and explicit theory. Cancer cells are derived from normal cells by somatic mutation followed by clonal selection. The somatic mutation must either give the mutated cell an advantage in growth rate or must bring it within one step of such an advantage. Virus particles can cause an equivalent change by adding genetic information to the cell, possibly in a manner similar to bacterial transformation or transduction. Following its initiation, the evolution of the cancer cell clone is a random process of selection similar to Darwin's concept of the evoluton of the species.

Burnet illustrated the incidence of somatic mutation in mammals with the story of fleece mosaic. About 30 out of 20 million Australian sheep have varying patches of long wool on their skin, and study indicates that this is due to a somatic mutation occurring at the rate proposed by Burnet as responsible for cancer. Like the theory of Armitage and Doll, Burnet's theory successfully accounts for the age incidence of common types of cancer. Burnet doubted the viral etiology of such cancers.

Physical Carcinogenesis

Physical carcinogenesis, as reported by E. T. and B. S. Oppenheimer *et al.* (New York) is a highly significant development. A thin solid sheet of any material—be it plastic, glass, parchment, mica, or metal—will produce from 5 to 55 percent incidence of malignant tumors (mainly fibrosarcomas) when imbedded subcutaneously in rodents. Initially, the sheet causes a rapid growth of fibroblasts around it; this slows up after 3 months and results in a thick pocket of inactive fibroblasts after 6 months. If cancer develops, it starts later, within an occasional isolated patch of reactivated fibroblasts. These patches usually arise near the inner surface of the pocket but may fail to appear. On the other hand, with woven fibers or powders of the same materials, there is often liberal fibroblastic growth, but no true pocket is formed and the tumor incidence is under 1 percent. Thus, the relevant feature is the physical form of the obstructing material. More important, one might deduce that the physical form of the fibroblastic pocket, rather than the mere presence of fibroblastic proliferation, initiates carcinogenesis.

Chemical Carcinogenesis

Chemical carcinogenesis was discussed by C. Heidelberger (Madison, Wis.), who presented evidence for a direct relation between the carcinogenicity and the degree of protein-binding of a skin carcinogen. But I. Berenblum (Rehovoth, Israel) thought that protein binding of the metabolites of a carcinogen may be nonspecific and questioned whether the original compound or a metabolite is the relevant carcinogen. He thought that dissection of the carcinogenic process into an "initiating" and a "promoting" phase has aided precise study, while P. Shubik (Chicago) thought a single-stage process applied.

The possible relation between occupational and spontaneous bladder cancer was highlighted. Bladder cancer was reported in 85 French workers exposed to aromatic amine dyestuff intermediates (J. L. Billiard-Duchesne, Rouen, France), in 16 American workers who had suffered long-term exposure, and in six other American workers who had been briefly or intermittently exposed (W. F. Melick, St. Louis). A better solution than routine cystoscopic examination for such workers is elimination of the manufacture of the responsible carcinogens, which include 2-naphthylamine, benzidine, and xenylamine. According to G. M. Bonser (Leeds, England), the active carcinogens are the orthohydroxy metabolites of these amines. Such orthoaminophenols are also produced spontaneously in man as normal metabolites of tryptophan, and E. Boyland (London, England) found that some of these are bladder carcinogens in mice. In man, these orthoaminophenols are rapidly conjugated by the liver and excreted in urine. While in the bladder, the inactive glucuronide conjugates are hydrolyzed by β-glucuronidase and thus become free to cause bladder cancer. Boyland found that most men with bladder cancer excrete more such orthoaminophenols and more β-glucuronidase than do normal subjects, and expressed the hope that bladder cancer might be prevented by inhibiting urinary β-glucuronidase with an oral drug. R. R. Brown and J. M. Price (Madison, Wis.), on the other hand, found that about 50 percent of patients with spontaneous bladder cancer had an abnormal tryptophan metabolism, but so also did 50 percent of patients with cancer of other sites. In most patients of both series, this abnormality could be partly corrected by administration of vitamin B_6. Brown thought that certain tryptophan metabolites that appear in human urine may have a causal significance in spontaneous bladder cancer, but other exogenous and endogenous factors are also relevant. In this context, J. Clemmesen (Copenhagen) reported that cigarette smoking is an important additional factor.

Lung Cancer

Lung cancer is the only common type of cancer whose incidence has rapidly increased in recent years. Unanimous agreement regarding certain aspects of this problem was demonstrated by congress lecturers.

L. Kreyberg (Oslo) reported that lung cancer can be divided into two histological groups: group I tumors, comprising mainly epidermoid and undifferentiated carcinoma, with an incidence related to external irritants and especially to cigarette smoking; and group II tumors, comprising mainly adenocarcinoma, with equal incidence in males and females and in rural and urban areas. While W. C. Hueper (Bethesda, Md.) disagreed that the incidence of group I tumors is related to cigarette smoking, W. Haenszel and M. B. Shimkin from the same institute used Kreyberg's classification to show that the incidence of group I tumors in women rises with the amount of cigarette smoking, just as other studies have shown this to be true for men. They found that the incidence of lung cancer in nonsmokers is roughly the same in men and in women. Their results indicate that the main disparities in lung-cancer death rates of men and women are resolved when smoking habits are considered. The authors noted that their study, the largest with female

subjects to date, agreed with the only other three sizable studies of this type so far published.

R. Doll (London, England) reported agreement between the results of his large prospective and retrospective studies: The incidence rate of lung cancer is over ten times as high in the average cigarette smoker as in nonsmokers, and the risk is proportional to the number of cigarettes smoked daily and increases with duration of the habit. For those who have stopped smoking for over 10 years, the rate is one-quarter that for persistent smokers. Similar results were reported by H. F. Dorn (Bethesda, Md.) for a prospective study among 290,000 American men: The incidence rate of lung cancer is over nine times as high in the average cigarette smoker as in nonsmokers, and cigarette smokers have a better chance of avoiding lung cancer if they stop smoking. E. L. Wynder (New York) reviewed his epidemiological studies and the evidence on experimental induction of lung cancer with tobacco smoke. On both counts, he has long since considered cigarette smoking established as the primary cause of lung cancer.

Regarding air pollution as an etiological factor in lung cancer, R. E. Waller (London, England) reported that there is a 2/1 ratio in over-all mortality from lung cancer in large towns as compared with rural areas in Britain. He suggested that part of the difference in lung-cancer mortality between urban and rural areas hitherto attributed to air pollution is only temporary in nature and reflects a later onset of cigarette smoking in the more rural areas. However, the data of P. Stocks (Colwyn Bay, Wales) indicated clearly that the relatively heavy atmospheric pollution in certain British cities is a major factor responsible for this urban-rural difference.

In a symposium on lung cancer, data of E. C. Hammond were quoted which show that the lung-cancer death rate of cigarette smokers in large American cities is five-fourths of that in rural areas. One possible explanation for this difference is that urban atmospheric pollution contributes an extra one-fourth as much risk as cigarette smoking. On this basis, an urban nonsmoker should have one-fourth the lung-cancer rate of an average cigarette smoker, and this fits Hammond's figures. His data show that the lung-cancer rate for nonsmokers in rural areas is very low, about 1/30 that of smokers. These considerations explain the findings of Stocks that lung-cancer rates increase faster with increase in cigarette smoking in rural areas than in cities: the lung-cancer incidence in rural nonsmokers is low enough for habitual smoking of even a few cigarettes to have a marked effect on lung-cancer rates (*1*).

Experimental evidence on air pollution was given by Hueper, who cited industrial dusts containing chromates, nickel, arsenic, asbestos, iron oxide, and possibly beryllium as carcinogenic for man. In addition, combustion products from coal, wood, and gasoline are carcinogenic. From these data, from the pathology of occupational lung-cancers, and from consideration of lung-cancer rates in cities in the United States without reference to individual smoking habits, he concluded that atmospheric pollution is a more important factor than smoking, although he agreed that cigarette smoking is a cause of lung cancer. P. Kotin (Los Angeles) concluded from laboratory studies that the environmental carcinogens responsible for lung cancer include polluted atmosphere, infectious agents, and cigarette smoke. L. M. Shabad (Moscow) reported that atmospheric pollution may be one of the causes of lung cancer, and that use of advanced fuel-burning systems and rational city plannng can decrease or prevent atmospheric pollution by 3,4-benzpyrene.

Experimental evidence on cigarette smoke was given by P. R. Peacock (Glasgow), who produced lesions of the respiratory tract in domestic fowls after 2 years of directing cigarette smoke thrice weekly into their buccal cavities. J. W. S. Blacklock (London, England) obtained lung tumors in two out of eight rats by inoculating the condensate from cigarette smoke directly into the lung substance. S. Neukomm and J. Bonnet (Lausanne, Switzerland) reported exact figures for the content of the powerful carcinogen 3,4-benzpyrene and of four other aromatic carcinogens in tar from cigarette smoke.

As for the future, J. Clemmesen calculated that if the present trend continues, then by 1990 the male lung-cancer incidence in Copenhagen will equal the 1950 figure for male cancer of all other sites together, and this increase will be due almost entirely to cigarette smoking, since Copenhagen has practically no atmospheric pollution.

The conclusion drawn here is that all investigators reporting epidemiological studies of the effect of cigarette smoking on lung-cancer incidence agreed unanimously that cigarette smoking is the main cause for the present increase in this disease (*2*). Also, all investigators reporting experimental studies in which cigarette smoke was specifically studied for carcinogenic effects agreed unanimously that cigarette smoke is a carcinogen for man (*2*). From these two sets of agreements it follows that the papers presented establish decisively that cigarette smoking is *a* cause of human lung cancer, and, beyond reasonable doubt, that cigarette smoking is the *main* cause of the present increase in lung-cancer incidence. After smoking, atmospheric pollution emerged as the most significant carcinogen. Epidemiological reports suggested that its effect is smaller but certainly not negligible, even relative to the powerful effect of habitual cigarette smoking; that, for nonsmokers, the incidence rate of lung cancer is very small in rural areas; and that atmospheric pollution greatly increases this rate.

Radiation

Radiation carcinogenesis was discussed at several symposia. H. S. Kaplan (San Francisco) thought that any tissue injury that leads to a disturbance in normal tissue regulatory mechanism may cause cancer. If the repair mechanism is unable to redress the injury, equilibrium is lost and cancer may result. Kaplan found that cancer may develop in a normal thymus retransplanted into an irradiated thymectomized animal; this suggests that total-body irradiation can have humoral effects. On the other hand, J. Furth *et al.* (Boston) reported that head irradiation is as effective as total-body irradiation in producing pituitary tumors in mice, and that these tumors are mostly adrenotropic, while most spontaneous pituitary tumors are mammotropic. Furth concluded that pituitary irradiation causes a tumorigenic change which might be a mutation but that actual development of the tumor depends on stimuli from pituitary-dependent organs.

A symposium on the carcinogenic risk of radiation, held under the chairmanship of W. C. Moloney (Boston), developed into a round-table discussion of whether a threshold exists for radiation carcinogenesis in man and whether there is a straight-line relationship between radiation dose to bone marrow and incidence of leukemia. Opinions were divided, and the discussion served notice that these questions delineate a major area of future controversy.

W. B. Looney *et al.* (Bethesda, Md.) established a link between Thorotrast administration and the occasional development of a rare type of liver tumor, which had a mean latent period of about 15 years in nine patients, and C. M. Gros *et al.* (Strasbourg) reported another such case. Yet C. Johansen (Copenhagen) found no liver tumors in 250 patients who had received Thorotrast from 10 to 20 years earlier but thought evaluation premature, since he found similar liver tumors late in the life of animals injected with Thorotrast. Lastly, N. Petrov *et al.* (Leningrad) induced osteogenic sarcoma in monkeys by bone-marrow injections of radium bromide.

Hormones

Hormonal carcinogenesis in endocrine-dependent organs, according to Sir C. Dodds (London, England), can be caused by an alteration of the natural

hormone background due to ablation of endocrine organs, application of an active hormone, or inborn abnormalities. O. Mühlbock (Amsterdam) thought the alteration that results in cancer of the "target" organ usually exposes it to an excess of a growth-stimulating hormone (that is, pituitary tropic hormones and sex hormones); thus, excess of a hormone can be carcinogenic for the "target" organ, while deficiency usually causes atrophy but not cancer.

These theories can be tested against experimental results reported at the congress. A. Lipschutz (Santiago, Chile) used mice to confirm his finding that subtotal castration produces tumors in sex organs towards the end of the natural life-span. The carcinogenic effects of long-term injections of large doses of sex hormones were documented by H. Kirkman (San Francisco) for testosterone proprionate in the Syrian hamster; by N. Petrov *et al.* for estrogens in monkeys; and by W. U. Gardner (New Haven, Conn.) and R. L. Noble and J. H. Cutts (London, Canada) for estrogens in mice. F. Bielschowsky (Dunedin, New Zealand) noted that when the concentration of thyroid hormone falls below a critical level, increased pituitary secretion of thyroid-stimulating hormone results. If the thyroid cannot respond, the pituitary continues its excess secretion; this results first in goiter and often eventually in cancer of the "target" organ.

Mammary tumors in mice were linked to hormonal, as well as to viral, stimulation. Thus, L. M. Boot and O. Mühlbock (Amsterdam) reported that subcutaneous transplantation of whole pituitaries into mice free from the milk factor caused induction of mammary tumors. R. E. Kavetsky *et al.* (Kiev, U.S.S.R.) found that the release of mammotropic and gonadotropic hormones during the estrus cycle followed a "disturbed" pattern in mice of the high-mammary-tumor strain C3HA. Experimental neuroses caused by running a 5- to 20-volt electric current through the cage floor altered pituitary gonadotropic activity and lowered the age of tumor incidence from 11 to 8 months. J. J. Bittner (Minneapolis) also found evidence for an inherited hormonal pattern associated with mouse mammary cancer and discussed transmission of the milk factor by the male mouse, while H. B. Andervont (Bethesda, Md.) confirmed the occasional spontaneous disappearance of the mammary agent from a mouse of high tumor strain.

Viruses

Viral carcinogenesis was a stimulating field for participants at the congress. A. M. Prince (New Haven, Conn.) reported that cancer induction by Rous sarcoma virus cannot be explained on a transduction model. P. Vigier (Paris) thought that Rous sarcoma grows in sensitive hosts more by reinfection of cells than by division of infected cells. New viral tumors included a deer fibroma and a superficial tumor in monkeys. C. Friend (New York) reported a new leukemia-like disease of mice and prepared a Formalin-inactivated vaccine that immunized 80 percent of the mice.

S. E. Stewart *et al.* (Bethesda, Md.) reported that a mouse-leukemia agent, after tissue culture for 2 weeks and subsequent inoculation into newborn mice, produced multiple types of neoplasms in from 60 to 100 percent of two different strains of mice. All mice with neoplasms had tumors of the salivary glands, and many had up to eight other types of unusual primary tumors, including sarcomas of the heart, kidneys, and subcutaneous tissues. Mice could be completely protected against the agent by passive immunization with rabbit antisera. R. Latarjet (Paris) found that injection of leukemic tissue extracts into isologous newborn mice accelerates the appearance of leukemia and occasionally results in unusual multiple primary tumors. A Graffi (Berlin-Buch, Germany) confirmed the finding that cell-free extracts of various transplantable mouse leukemias produce a high incidence of myeloid leukemia when injected into newborn mice, while J. Rygård (Copenhagen) demonstrated that phagocytosis is low in leukemic and in newborn mice.

In his abstract, L. Gross (New York) reported the induction of leukemia in up to 50 percent of a low-leukemia strain of mouse by fractionated doses of x-rays. Cell-free extracts of the leukemic tissues were injected into newborn mice of the same strain and caused an 11-percent incidence of leukemia as compared with a 0.5-percent incidence with cell-free extracts of normal tissues. However, the incidence of parotid tumors was respectively 5 and 7.5 percent in the two groups. Gross thought that mice of a low leukemic strain may carry a latent leukemic agent of low pathogenic potential which may induce leukemia in its carrier host when triggered by ionizing radiation. D. Metcalf and R. Buffett (Melbourne and Boston) found that the pathogenesis of lymphatic leukemia induced by radiation in mice of low leukemic strain is similar to that occurring spontaneously in mice of high leukemic strain. These two papers provide experimental evidence for an alternative to Burnet's interpretation—that, although the age incidence of acute leukemia in man is compatible with a viral etiology, such etiology is unlikely, since radiation can induce leukemia.

No slides of electron micrographs were shown to substantiate the claim of A. D. Timofejevsky (Moscow) that extracts of from 40 to 50 percent of various human malignant solid tumors contain round virus-like bodies, but an article was available for inspection that contained two pictures of controversial value.

Biochemical Characteristics

The cancer cell was discussed by V. R. Potter (Madison, Wis.), who gave biochemical meaning to the somatic mutation theory of cancer. He thought that mutation of a gene (deoxyribonucleic acid) results in the loss of specific enzyme-forming systems controlling the inhibition of cell division by a negative feedback mechanism. Gene mutations may show up directly as loss or change of enzymes or cell surface antigens, or may involve enzyme-forming mechanisms (ribonucleic acid), with the same final result. Potter thought that no unique over-all enzyme pattern characteristic of cancer tissue had so far been demonstrated, and that the total picture includes electron transport, carbohydrate metabolism, and nucleic acid synthesis.

S. Weinhouse (Philadelphia) thought, in contradiction to Warburg's theory, that there was no respiratory impairment in tumors but noted that tumor cells have a voracity for glucose. While many quantitative differences between normal and tumor tissues exist, no unique differences in pathways of electron or carbon transport or substrate utilization had been demonstrated. He thought that an enzyme activity may be low or absent in specific tumors, but knowledge of the same system in the normal tissue of origin and in other tumors was lacking. This point was illustrated during the congress by the report of G. Weber and A. Cantero (Montreal) that glucose-6-phosphatase activity is absent in Novikoff hepatoma, while Z. Albert *et al.* (Wroclaw, Poland) reported its virtual absence in Crocker sarcoma and mammary adenocarcinoma but its presence in a chrysoidin-induced mouse hepatoma.

Among those who presented experimental papers, D. Burk *et al.* (Bethesda, Md.) reported that the majority of clinical cancer chemotherapeutic agents are strong inhibitors of one or both processes of glycolysis and respiration. From this primary inhibition, secondary effects may result, such as deranged nucleic acid and coenzyme synthesis, or cell breakdown and death. Burk found a good correlation between clinical response and metabolic effects and concluded that the method of metabolic analysis presented by him and his coworkers offers a promising new approach to the selection of agents for clinical trial. S. Graff *et al.* (New York) reported on tumor growth inhibition when the acclimatized host is kept under hypoxia. They thought that this inhibition was due to the inability of tumors to become acclimatized, since even under normal oxygen tension the

high glycolytic rate of cancer cells was a consequence of the inadequacy of normally constituted respiratory processes to keep pace with the exorbitant capacity of tumors for replication.

Metabolism

The metabolism of tumors was discussed by P. Emmelot (Amsterdam), who found that the endogenous respiration of ascites tumor cells is mainly due to oxidation of cellular fatty acid, while D. M. Watkin (Bethesda, Md.) noted that there is an increased utilization of body fat in human cancer patients and thought that this is responsible for the negative caloric balance of patients with active cancer. R. E. Greenfield and V. E. Price (Bethesda, Md.) reported that the anemia of tumor-bearing animals is due to blood destruction through vascular lesions in the area of the tumor, while W. Nakahara (Tokyo, Japan) found that tumor depresses the liver catalase activity of its host by interfering with the utilization of iron in the synthesis of catalase. A possible inference from these two papers is that the depression of liver catalase activity in tumor-bearing animals is partly due to a deficiency of iron for catalase synthesis.

In the area of protein synthesis, P. C. Zamecnik *et al.* (Boston) reported that soluble ribonucleic acid is directly involved in the sequence of enzyme reactions leading from free amino acid to protein. The synthetic pathway is similar for normal rat liver and for mouse Ehrlich ascites tumor. H. Busch *et al.* (Chicago) found that synthesis of the histone fraction of nuclear proteins from L-lysine occurs from three to ten times faster in two transplantable tumors than in normal rat tissues. Regarding radiosensitizers, F. Seelich (Vienna) reported that hematoporphyrin and related substances potentiate the action of x-ray on Ehrlich mouse ascites cells in vitro, while hematoporphyrin has a protective effect against a lethal dose of x-ray in vivo.

Transplantation

Transplantation of tumors is vital for biochemical and therapeutic studies. W. B. Patterson (Boston) reported a successful heterotransplant into the cheek pouch of cortisone-treated hamsters of a malignant melanoma excised from a patient who is now without evident tumor. Chemotherapeutic experiments have been run on the heterotransplant to determine its susceptibility to hormones and nitrogen mustard, for reference in case the patient develops metastases. The method is yet of limited application, since in Patterson's study only one-third of the tumors specially selected for high growth potential would take. H. E. Pogosianz *et al.* (Moscow) reported use of the steppe lemming for biological experiments. This rodent is somewhat similar to the mouse, and mouse sarcoma 180 will grow in from 80 to 90 percent after subcutaneous transplantation. Work on inbreeding is in progress.

Tissue Culture

Tissue culture was used by K. K. Sanford *et al.* (Bethesda, Md.) to show that a clone of cells originally derived from one cell of normal subcutaneous connective tissue of a strain C3H mouse can undergo neoplastic transformation in vitro. G. O. Gey *et al.* (Baltimore) noted that human tumor cells respond less easily to tissue culture than do normal lung cells.

Cytology

In the area of cytology, C. E. Ford and R. H. Mole (Harwell, England) reported that while normal tissues show a high degree of chromosomal constancy, with only 1 in about 500 mitoses showing deviation from the normal diploid number of 40, most reticular neoplasms show much less constancy and often have a slightly greater diploid number. From one to six distinctive new chromosomes may be present as a characteristic feature of the chromosome set and remain unchanged through serial passage; this suggests that each is genetically unique. In this connection, B. M. Richards and N. B. Atkin (London, England) found that the ratio of deoxyribonucleic acid content to chromosome number is generally significantly greater in tumors than in normal epithelia.

Immunology

The immunology of tissue antigens is an area in which rapid advances are being made. Since it seems easier to exploit a gain rather than a loss in antigenicity of the cancer cell, the report of L. Sachs (Rehovoth, Israel) was welcome. All homotransplantable tumors that he has investigated have gained antigenicity in comparison with the tissue from which they were derived, irrespective of whether or not they have lost agglutinogens. Regarding loss of antigens, H. N. Green (Leeds, England) thought that cancer results from a cytoplasmic deficiency of a lipoprotein complex which contains the tissue-specific antigen. Similarly, E. Weiler (Pasadena) said that the kidney-specific antigen is lost during carcinogenesis. In contrast, L. A. Zilber (Moscow), working with liver and hepatoma, thought that tumors do not lose their tissue-specific antigen. However, other antigens of normal tissues may be absent in tumors and, conversely, some tumors may contain additional antigens.

Preferential in vivo localization of I^{131}-labeled antibodies in isologous and homologous tumors was reported by D. Pressman and E. D. Day (Buffalo) and by I. L. Spar *et al.* (Rochester). Pressman concluded that the tumors tested contain identical or cross-reacting antigens which are either absent or present to a very small extent in normal tissues. Regarding the cytotoxic effects of rabbit antisera with respect to mouse lymphoma cells, J. G. Kidd (New York) found enhancement by normal guinea-pig serum; this serum was also effective alone, presumably due to its content of complement. On the other hand, R. Willheim (New York) ascribed the strong cytotoxic effect of normal human serum against mouse Ehrlich ascites cells to properdin, since zymosan abolished the effect.

E. J. Ambrose and G. C. Easty (London, England) showed a fascinating film of cell movements of normal fibroblasts and sarcoma cells in tissue culture, using the new interference microscope. The film showed that normal cells readily form permanent adhesions with their neighbors which restrict their movement, while cancer cells do not, and the latter move freely over normal cells and over each other. The change from normal to tumor cell is accompanied by a decrease in mutual adhesiveness of the cell surface and continues progressively as the tumor becomes more anaplastic. During the change, the cells become progressively more negatively charged. Thus, acquisition of decreased cell adhesiveness and increased negative charge seems to be characteristic of the neoplastic transformation and of tumor progression.

Detection

Since chances for a complete cure are highest while the cancer is still small and localized, L. T. Coggeshall (Chicago) thought the originators of the American Cancer Society acted wisely in 1913 when they fixed as one of their major goals the education of "the public in the absolute necessity of treatment at the earliest indication of cancerous growth." According to G. Pifher (Toronto), more people would seek early diagnosis if cancer education presented the facts of the disease in a positive manner, to popularize a more hopeful attitude towards the disease. M. Donaldson (Oxford, England) concluded that cancer education will save many lives and quoted Emerson's saying that "knowledge is the antidote to fear."

The physician is aided in cancer diagnosis and therapy by receiving specialized training at all professional levels, and by help with respect to provision of adequate physical facilities and specialized equipment. According to N. P. Duany (Havana, Cuba), these vital services depend on the financial resources available in each country for the fight against cancer. He thought a continuous educational campaign should be carried on through lectures, films, symposia, and journals, and that anticancer centers, de-

tection clinics, and cytological laboratories should be set up. It was good to hear from J. R. Heller (Bethesda, Md.) that in the United States these programs are being directly carried out or financially supported through the cooperative efforts of the American Cancer Society and the National Cancer Institute of the U.S. Public Health Service. Perhaps most important, progress is being assured through increasing support of cancer research.

Exfoliative cytology was stressed as being of high life-saving value, because it permits diagnosis of cancer at an early stage. For cancer of the cervix uteri, H. Yagi (Okayama, Japan) reported that a triphenyltetrazolium chloride stain was superior to Papanicolaou's staining method. A diagnostic rate of about 1 in 300 unselected patients was reported by H. C. McLaren (Birmingham, England), which agrees with D. A. Wood's figures for cervical-cancer screening programs in the United States. A. F. Anderson (Edinburgh) reported a rate of 1 in 70 for a group of 1000 patients without symptoms but referred by private practitioners. In achieving maximal diagnostic accuracy, J. E. Ayre (Miami) found that histological confirmation of positive smears was valuable.

For 500 patients with lung cancer, L. V. Ackerman and H. J. Spjut (St. Louis) found that bronchial biopsies were positive only for 28 percent, as compared with positive findings for 60 percent if exfoliative cytology was used and for 80 percent if three or more cytological examinations were made. Cancer cells were often found in pleural washings after incision biopsy; this suggests that tumor cells may have seeded the pleural surface. No diagnostic errors were found to have been made in 48 operations performed on the basis of positive clinical, radiographic, and cytological findings but negative bronchial biopsies. Similarly, D. S. Rome (Albany) reported a diagnostic accuracy of from 65 to 85 percent with exfoliative cytology.

In the cytological examination of gastric washings, J. B. Duguid (Newcastle-upon-Tyne, England) improved to over 90-percent accuracy with experience. He had initial difficulty with cells appearing in chronic atrophic gastritis, which were almost indistinguishable from carcinoma cells. For cytological diagnosis of cancer of the esophagus, O. T. Messelt (Oslo) obtained 90-percent accurate results. G. N. Papanicolaou (New York) believes that exfoliative cytology also shows great promise for diagnosis of cancer of the rectum and bladder and of the pleura and peritoneum.

W. H. Cole *et al.* (Chicago) and G. E. Moore *et al.* (Buffalo) both reported that about 30 percent of patients with disseminated cancer have cancer cells in the peripheral circulation. For "curable" patients, Cole's figure was 17 percent, while Moore's figure was somewhat lower. Both teams of workers found that surgical operation for removal of the cancer sometimes stimulated release of cancer cells. M. Lenz (New York) studied circulation in the tumor bed and concluded that richly vascularized tumor beds are best equipped to spread cancer. He thought that especially wide fields of treatment should be used with cancer growing in richly vascularized tissue.

Surgical biopsy, according to W. Boyd (Toronto) and G. Gricouroff (Paris) must be the means of determining whether a doubtful lesion is a tumor and, if so, whether it is benign or malignant, localized or invasive, operable or inoperable, radiosensitive or not. The role of surgical biopsy as a disseminating factor in cancer of the breast, unless immediately followed by surgical treatment, was clearly documented by C. Sayago and D. Sirebrenik (Santiago, Chile). In a group of 40 cases in which an average delay of 33 days occurred between a positive surgical biopsy and radical mastectomy, the five-year survival rate was 22 percent. In a second group of 40 cases where biopsy was immediately followed by radical mastectomy, the five-year survival rate was 85 percent.

P. B. Hudson (New York) reported an 11 percent incidence of prostatic cancer in a random sample of 800 men above 45. As a result, Hudson strongly recommended treating prostatic enlargements by surgical operations, which are chosen after a frozen-section diagnosis of the posterior prostate has been made. J. S. Lott *et al.* (London, Canada) used small-needle biopsy to prepare cytological smears on albumin-covered slides. The method was useful for breast tumors, secondary lymph-node metastases, and soft-tissue tumors.

While x-ray examination is a most valuable diagnostic tool, the use of chest x-ray screening programs remains controversial. For Norway, where 16 percent of the civilian population is screened each year, H. Höst (Oslo) reported that one new case of primary lung cancer is discovered per 13,000 chest x-rays. This rate of discovery adds up to 10 percent of all new cases, while about 60 percent of these new cases had had at least one mass x-ray examination within the preceding 4½ years. This does not imply that five-sixths of the cases were missed, since most cancers must have enlarged in the interval between x-ray examination and diagnosis.

In the area of clinical laboratory tests for diagnosis of cancer, W. H. Fishman (Boston) reported, from a study of 100 patients, that measurement of the serum acid phosphatase that is sensitive to inhibition by L-tartrate provides the best laboratory indicator for cancer of the prostate, since the level is often elevated even in nonmetastatic cancer of the prostate. D. W. Molander *et al.* (New York) noted that elevated serum glutamic oxalacetic levels are useful in the diagnosis of hepatitis in icteric patients with lymphomas or other neoplastic disease.

Distribution

Population studies showed that cancer is becoming more common as medical science raises the life-span of man. Thus, V. A. Marcial (San Juan, Puerto Rico) reported that in 1930 the average life expectancy of Puerto Ricans was 40 years and that cancer was the seventh cause of death. Today, the life expectancy is 68 years, and cancer is the second cause of death.

Valuable clues to the causes of "spontaneous" cancer can emerge from studies of cancer distributions in different geographical locations and ethnic groups. J. N. P. Davies (Kampala, Uganda) reported that leukemia is much less frequent in African peoples than in Europeans, while the incidence of lymphomas is higher; this suggests that the etiology of these lesions differs in Africans and in Europeans. Similarly, K. Takeda (Sapporo, Japan) reported a lower rate of leukemia in Japan (about one-third to one-half the rate in Western countries and in the United States) and also an unusually low proportion of chronic leukemias. Regarding differences in cervical cancer rates of different ethnic groups, a cooperative study between J. Casper (Petah Tiqvah, Israel) and L. J. Dunham *et al.* (Bethesda, Md.) showed identical incidence rates in Jewish women living in Israel and in New York. The incidence rates for New York residents from other ethnic groups were four times higher for non-Jewish women, 11 times higher for Negro women, and 23 times higher for Puerto Rican women. The study failed to confirm the theory that lack of circumcision of the male partner is associated with cancer of the uterine cervix.

Therapy

Surgical treatment of cancer was discussed by J. F. Nuboer (Utrecht. Holland), who thought that the recent advances have not resulted from improvement in surgical technique but from the help obtained from the basic sciences. O. H. Wangensteen (Minneapolis) reported experiences with routine "second look" operations, performed at intervals of six months until a negative look is obtained. In 165 patients operated upon for cancer of the stomach, colon, or rectum, one-half still had cancer at the first reexploration; in 11 percent of this group negative findings were eventually achieved after reoperation. In the other one-half—patients who were apparently

without cancer at the time of reexploration—21 percent eventually died of cancer. The salvage rate of 5.5 percent for the whole group was offset by an equal mortality rate for the "second look" operations; however there were no deaths in cases declared negative on the first reexploration. Wangensteen concluded that the program has shown clearly how extensive the primary operation should be.

For carcinoma of the corpus uteri, W. Hawksworth (Oxford, England) reported an operability rate of 88 percent and a five-year survival rate of 64 percent; the nodes of the lateral pelvic walls are a common site for recurrence. R. M. Fawzy (Cairo, Egypt) noted that bladder cancer comprises 40 percent of cancer in Egypt, possibly because of predisposition to infestation by *Bilharzia*; the operability rate is under 10 percent, with a five-year survival rate of 30 percent. R. Schade (Newcastle-upon-Tyne, England) thought that carcinoma of the stomach develops nearly always in a diseased gastric mucosa and especially in association with chronic atrophic gastritis.

Radiation therapy of cancer, according to F. Baclesse (Paris) has been improved to deliver an increased dose of radiation to the tumor. This is achieved by physical means, such as rotation, convergence, or grill therapy, and by biological means such as dose fractionation, and high voltage sources are valuable. For conventional x-ray therapy of lung-cancer patients with tumor doses up to 5000 r, S. Mustakallio (Helsinki) reported a five-year survival rate of 2 percent in patients with advanced disease and of 26 percent in a small proportion (3 percent) selected for surgery and postoperative x-ray treatment. L. Larsson *et al.* (Stockholm) found that colloidal Au^{198} is taken up by bone marrow only in places of active hematopoiesis. Use of an automatic scanning scintillation counter to obtain bone marrow scintigrams gave valuable information in treatment of chronic leukemia, bone marrow carcinosis, and polycythemia vera.

Endocrine management of cancer of the thyroid has shown spectacular progress, as summarized in exhibits by E. E. Pochin and K. E. Halnan (London, England), L. G. Larsson (Stockholm), and J. C. McClintock (Albany). The therapist has now at his command the surgical techniques of lobectomy, total thyroidectomy, and radical neck dissection, which can be followed by external irradiation. In metastatic thyroid carcinoma, radioiodine often greatly prolongs life; temporary administration of antithyroid drug may revive the functional activity of the tumor and thereby renew its uptake of radioiodine; thyroid hormone sometimes causes regression of hormone-dependent tumors; and external radiation helps to relieve pain.

For disseminated cancer of the breast, R. A. Huseby (Denver, Colo.) reported that adrenalectomy or hypophysectomy benefited one-third of the cases. He stressed the need for a method to predict the results of these operations and noted that for women who are menstruating regularly, failure to respond to castration often heralds failure to respond to androgens, to adrenalectomy, or to hypophysectomy. X-ray treatment and intracavitary colloidal Au^{198} are valuable, even for patients already on hormone therapy. Sir C. Dodds (London, England) reported that 30 percent of patients with disseminated breast cancer responded to ovariectomy; he questioned use of hypophysectomy because of high operative mortality. C. Huggins (Chicago) reported that 11 different procedures induce remission in hormone-dependent metastatic cancer of the breast. In two studies on hypophysectomy of patients with advanced lesions, the five-year survival rates were 0 and 4 percent, respectively. Huggins further developed the method of H. Shay *et al.* (Philadelphia) and induced hormone-dependent mammary tumors rapidly in a high percentage

of female rats with a single dose of 5 mg of methylcholanthrene, given by stomach tube; both Shay and Huggins used such tumors to assay hormonal and therapeutic agents.

Chemotherapy

Chemotherapy of cancer, according to T. Yoshida (Tokyo), is taking its place beside surgery and radiation as a unique weapon to prevent metastases and alleviate disseminated cancers. The five main classes of active compounds discussed were alkylating agents, nucleic and folic acid antagonists, quinones, antibiotics, and steroids. One rationale is to poison the cancer cell selectively, by exploiting the very differences that give it a biological advantage.

Nitrogen mustard, with the formula $CH_3—N—(CH_2—CH_2—Cl)_2$, often abbreviated to HN2, inhibits cell division by reacting with nucleoprotein but produces violent nausea. The less toxic and more soluble phenylbutyric acid derivative Chlorambucil was found to be superior for treatment of lymphocytic leukemias and lymphomas, in Europe and in the United States. Another amino acid (phenylalanine) derivative of HN2 named Sarcolysin was synthesized later independently in the Soviet Union and in England. N. Blokhin (Moscow) reported that Sarcolysin is effective for metastatic seminoma of the testicles but not for metastatic teratoma. Other HN2 derivatives mentioned include the HN2 mannitol compound Degranol, which gives regressions in metastatic cancer (P. Rubányi, Budapest); the N′O-propylene phosphate ester diamide of HN2 named "B-518," which has low toxicity and gives good remissions in lymphosarcomas (R. Gross and K. Lambers, Marburg, Germany); and several others, including drugs showing promise in animal experiments, such as the three-stage drugs formed by linking a two-stage HN2-amino acid derivative like Sarcolysin with another amino acid, vitamin, or nucleic acid precursor (L. F. Larionov, Moscow). Alkylating agents other than HN2 and its derivatives include Myleran, which is effective in treatment of generalized myeloid leukemia or in the radiation-resistant disease (D. A. G. Galton and P. E. T. Hancock, London, England); and *dl*-diepoxybutane, which shows promise in Hodgkin's disease (J. Bichel, Aarhus, Denmark).

C. P. Rhoads (New York) thought that cancer is a somatic mutation which causes changes in nucleic acid structure, and that these changes are the key to the peculiar properties of the cancer cell. Many chemotherapeutic compounds act by interfering with nucleic acid metabolism. Thus, 8-azaguanine is rapidly incorporated into tumor to form a nonfunctional ribonucleic acid molecule, while, according to P. Feigelson and J. E. Ultmann (New York), it also inter-

feres with nucleic acid metabolism by in vivo inhibition of xanthine catabolism. Similarly, C. Heidelberger reported that 5-fluorouracil and related analogs form nonfunctional (or "fraudulent") nucleic acids and also inhibit nucleic acid biosynthesis. A. R. Curreri (Madison, Wis.) found that 5-fluorouracil is clinically effective against tumors but also affects rapidly growing normal tissues, while R. Duschinsky *et al.* (Nutley, N.J.) had synthesized its riboside and deoxyriboside in the hope of reducing toxicity. J. R. Fountain (Leeds, England) found 6-mercaptopurine very useful for chronic myeloid leukemia, perhaps due to activation at a site other than tumor (E. J. Sarcione and L. Stutzman, Buffalo). E. Frei *et al.* (Bethesda, Md.) found 6-azauracil too neurotoxic, while A. D. Welch *et al.* (New Haven, Conn.) reported that its riboside is from 10 to 20 times as effective against mouse tumors. S. Farber (Boston) noted that antifolics act by inhibiting cofactors essential for biosynthesis of nucleic acid precursors and stressed the use of Aminopterin (4-aminopteroylglutamic acid) for acute leukemia in children and of the related Methotrexate for acute leukemia with lung metastasis.

Among quinones, the ethyleneiminoquinone "E-39" inhibits cell glycolysis (N. Gerlich and H. J. Wolf, Bielefeld, Germany) and often gives satisfactory remissions in metastatic cancer and chronic lymphomatoses (Wolf and Gerlich; J. Bernard *et al.*, Paris). Both Farber and C. T. C. Tan *et al.* (New York) reported favorably on use of actinomycin D with Wilms' tumors; Tan also had good results in children with neuroblastomas but not in adults with metastatic neoplasms. Steroid therapy in chronic lymphatic leukemia was stressed by B. R. Scott (London, England) and by J. G. Freymann and J. B. Vander (Boston); they noted especial benefit in the presence of severe and refractory anemia, but infections were a serious complication.

Ideally, all screening of compounds for cancer chemotherapy should be done in man (C. C. Stock, New York). Since this is impracticable, Stock thought that assay systems such as heterologous transplants of human tumors; spontaneous, induced, and transplantable animal tumors; and tissue cultures and cultures of microorganisms all have their place. With K. Sugiura, he used a new transplantable mouse-virus leukemia to screen 100 different compounds by the simple initial criterion of spleen weight in treated and control mice. R. Bather (Edinburgh) employed day-old chicks injected with Rous sarcoma virus to test antifolics, while A. Goldin *et al.* (Bethesda, Md.) used an advanced mouse leukemia as a rapid assay system.

For objective clinical evaluation of chemotherapeutic response, E. Paterson (Manchester, England) defined a remission as the time interval after treatment within which a clinical index had again risen to its pretreatment value. The index was calculated by assigning a score of 2 for improvement, 1 for unchanged condition, and 0 for advancing disease to each of ten clinical indications: superficial nodes, mediastinum, spleen, liver, effusions, hemoglobin, fever, well-being, weight, and ability to work. Using this method, Paterson showed precisely how the length of the remission decreased with each additional course of therapy in Hodgkin's disease.

Combination therapy of chemotherapeutic agents with x-rays was reported to give beneficial effects in Hodgkin's disease but not in leukemia (L. Heilmeyer, Freiburg, Germany). Several papers reported effective use of chemotherapy as an adjunct to surgery. L. F. Larionov thought that the antitumor effect of chemotherapeutic substances is inversely proportional to the mass of the tumor, hence that chemotherapy should be more effective when the tumor mass is small—a concept similar to that of Shimkin and Moore. Larionov reported that 18 patients were given HN2 or Novdembichin at an early stage of Hodgkin's disease: 50 percent survived for 5 years; 22 percent, for over 8 years.

Conclusion

In summary, a brief glimpse at the world-wide problem of cancer in 1958 is frankly heartening, showing steady advances on a widening front. Many speakers held that a single cure for cancer is unlikely and studied each group of cancers almost as a separate disease. Some hoped that cancer can be eradicated without an understanding of its very nature; others felt that we must understand better the enigma of the cancer cell and even of life itself. If the somatic mutation theory of cancer is right, then development of cancer is an inherent property of life, and cancer research is but in its lusty infancy. There is every hope that there will be continuing advances in understanding, detection, and therapy.

Thanks are due the British Organizing Committee for its excellent conduct of the congress and for its selection of the pleasant Royal Festival Hall and London County Hall as meeting places. The daily round of entertainments served to make the meeting truly memorable; these included a performance of Aida at Covent Garden Opera House, a delightful garden party at Hurlingham after a boat trip up the Thames, and a performance of the resplendent Guards bands under floodlights at Hampton Court palace.

At the closing session, V. R. Khanolkar (Bombay) was announced as president of the International Union Against Cancer, and A. Haddow (London, Eng-

land) as president-elect. The next International Cancer Congress will be held in the Soviet Union in 1962. In his closing speech the president of the present congress, Sir S. Cade, noted with pleasure the number of young scientists who had attended, saying he thought it augured well for the future.

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Notes

1. Application of Doll's findings of proportionality to Hammond's data suggests that smoking four cigarettes per day (about one-fourth the average cigarette consumption) will equal in effect the atmospheric pollution experienced in an average American city. It will therefore increase eightfold the low lung-cancer rate of rural nonsmokers, while doubling the rate for urban nonsmokers.
2. Checked by correspondence following the congress with authors of papers where any possible doubt of agreement existed.

Forthcoming Events

December

29–30. National Council of Teachers of Mathematics, New York, N.Y. (M. H. Ahrendt, NCTM, 1201 16 St., NW, Washington 6.)

29–17. Bahamas Surgical Conf., 1st, Nassau, Bahamas. (B. L. Frank, 1290 Pine Ave., W., Montreal, Canada.)

January

6. Society for Applied Spectroscopy, New York, N.Y. (P. Lublin, Sylvania Research Laboratories, Bayside, N.Y.)

7–9. Northeastern Weed Control Conf., 13th annual, New York, N.Y. (E. R. Marshall, Carbide & Carbon Chemical Co., New York, N.Y.)

12–14. Reliability and Quality Control, 5th natl. symp., Philadelphia, Pa. (W. T. Sumerlin, Philco Corp., 4700 Wissahickon Ave., Philadelphia 44.)

18–31. Bahamas Serendipity Session, Nassau, Bahamas. (B. L. Frank, 1290 Pine Ave., W., Montreal, Canada.)

20–22. American Mathematical Soc., annual winter, Philadelphia, Pa. (E. G. Begle, Leet Oliver Hall, Yale Univ., New Haven, Conn.)

21–22. American Group Psychotherapy Assoc., 3rd annual institute, New York, N.Y. (C. Beukenkamp, Public Relations Chairman, 993 Park Ave., New York 28.)

22–23. Mathematical Assoc. of America, 42nd annual, Philadelphia, Pa. (H. M. Gehman, MAA, Univ. of Buffalo, Buffalo 14, N.Y.)

23–24. American Group Psychotherapy Assoc., 16th annual conf., New York, N.Y. (C. Beukenkamp, Public Relations Chairman, 993 Park Ave., New York 28.)

23–24. Reproductive Physiology and Protein Nutrition, 15th annual conf. on protein metabolism, New Brunswick, N.J. (J. H. Leathem, Rutgers Univ., New Brunswick, N.J.)

24–29. American Acad. of Orthopedic Surgeons, Chicago, Ill. (C. L. Compere, 720 N. Michigan Ave., Chicago, Ill.)

26–29. American Meterological Soc., New York, N.Y. (K. C. Spengler, AMS, 3 Joy St., Boston 8, Mass.)

26–29. American Soc. of Heating and Air Conditioning Engineers, 65th annual, Philadelphia, Pa. (W. M. Vidulich, ASHACE, 62 Worth St., New York 13, N.Y.)

26–29. Institute of the Aeronautical Sciences, 27th annual, New York, N.Y. (IAS, 2 E. 64 St., New York 21.)

26–30. Writing and Publication in Industry, conf. and workshops, Brooklyn 1, N.Y. (T. L. Donahue, Writing and Publication Conf., Polytechnic Inst. of Brooklyn, 333 Jay St., Brooklyn 1.)

27–30. Society of Plastics Engineers, Inc., 15th annual tech. conf., New York, N.Y. (L. A. Bernhard, SPE, 65 Prospect St., Stamford, Conn.)

28–29. Nuclear Fuel Elements, 1st intern. symp., New York, N.Y. (H. H. Hausner, 1st intern. Symp. on Nuclear Fuel Elements, 730 Fifth Ave., New York 19.)

28–31. American Physical Soc., annual, New York, N.Y. (E. R. Fitzgerald, Dept. of Physics, Pennsylvania State Univ., University Park.)

29–31. Western Soc. for Clinical Research, 12th annual, Carmel-by-the-Sea, Calif. (W. N. Valentine, Office of the Secretary, Univ. of California Medical Center, Department of Medicine, Los Angeles 24.)

(See issue of 21 November for comprehensive list)