

SCIENCE

12 December 1958

Volume 128, Number 3337

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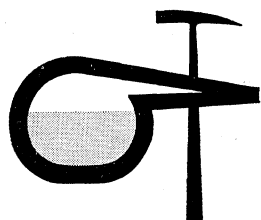
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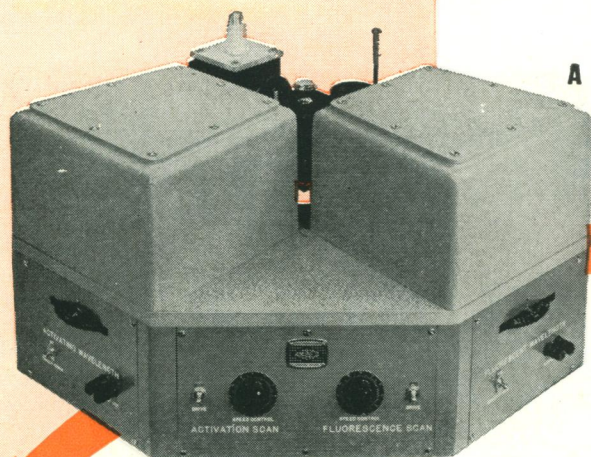
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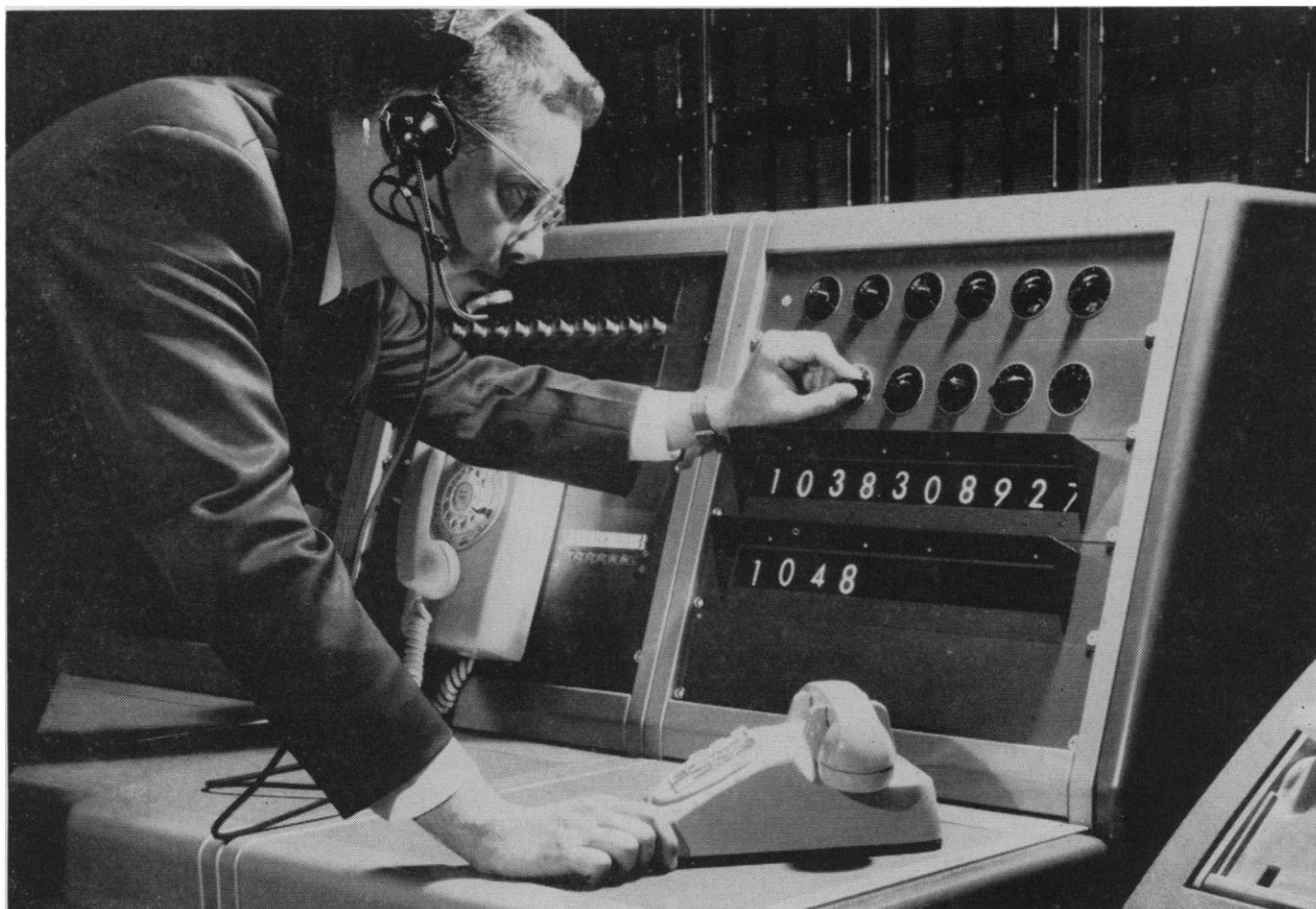
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Kodak Industrial X-ray Film, Type AA beats *KK* seven ways to Sunday for "radiographic sensitivity." It's some slower, though. As *Type A*, it used to be a lot slower. That was a little over a year ago. It was then the most widely used x-ray film in industry. Now it's more so. That sounds like tautology. Nevertheless, it makes us happy. With the higher speed, inherent contrast has gone up, not down. Grain's the same. This is remarkable.

They can just reduce exposure time. Even for thinner specimens, time is money. So it is said. Or they can cover more area at a single exposure. That's another way to save time.

Or they can take the same time and get more film density. Contrast

*Don't trip. "Sensitivity" doesn't mean "speed" here.

and therefore "radiographic sensitivity" improve at higher density.

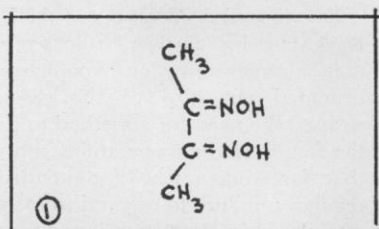
Or they can get through the specimen with less penetrating radiation. Softer radiation emphasizes density differences along ray paths of slightly different absorption. You want those differences.

Kodak Industrial X-ray Film, Type M is for maximum detail and no rush, or else light specimens. *Kodak Industrial X-ray Film, Type F* goes with calcium tungstate screens. Their fluorescence in the visible intensifies the exposure. In a pinch that's sometimes all right.

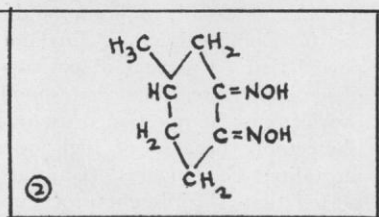
Don't worry. You'd get the hang of it if you had to. Yes, even the radiography of plutonium hardware, where you're recording both endogenous and exogenous radiation. We'd give you what advice we could (but very little about plutonium). You'd write Eastman Kodak Company, X-ray Division, Rochester 4, N. Y.

We also have some freshly minted advice on silver-sensitized goods for dosimetry, including a bibliography. If that's all you want, write Eastman Kodak Company, Special Sensitized Products Division, Rochester 4, N. Y. Ask for the new pamphlet, "Radiation Monitoring with Kodak Personal Monitoring Films." It's useful for processing techniques, if nothing else.

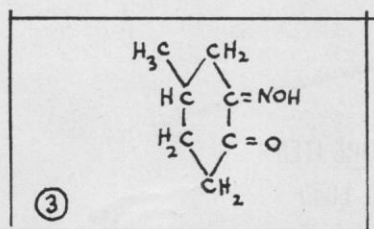
The isonitroso that wasn't expected



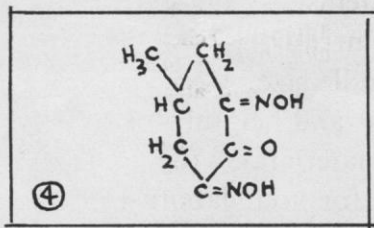
Dimethylglyoxime (Eastman 98), a rip-roaring success as a nickel reagent. Precipitate so beautiful that it's used in the lipstick trade.



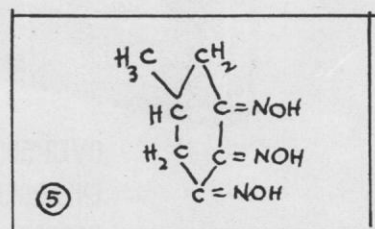
Reported recently by some fellows as an improvement. We want to make it, but we hate to mess around with selenium dioxide the way they did.



What we hoped to get reacting 4-Methylcyclohexanone (Eastman 3083) with iso-Amyl Nitrite (Eastman 436). It's common knowledge that an alkyl nitrite will isonitrosate a methylene adjacent to a carbonyl.



What we actually got. Nature appears to be bent on isonitrosating next to a carbonyl group, even at the expense of leaving some of the original ketone unreacted in case of insufficient nitrite.



Ketonic carbonyl oximated, by hydroxylamine. This part of the plan worked. We have put this in stock as 5-Methyl-1,2,3-cyclohexanetrione Trioxime (Eastman 7478). We hope somebody will discover what it is a reagent for.

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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. Wangenstein concluded that the program has shown clearly how extensive the primary operation should be.

For carcinoma of the corpus uteri, W. Hawsworth (Oxford, England) reported an operability rate of 88 percent and a five-year survival rate of 64 per-

cent; 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, accord-

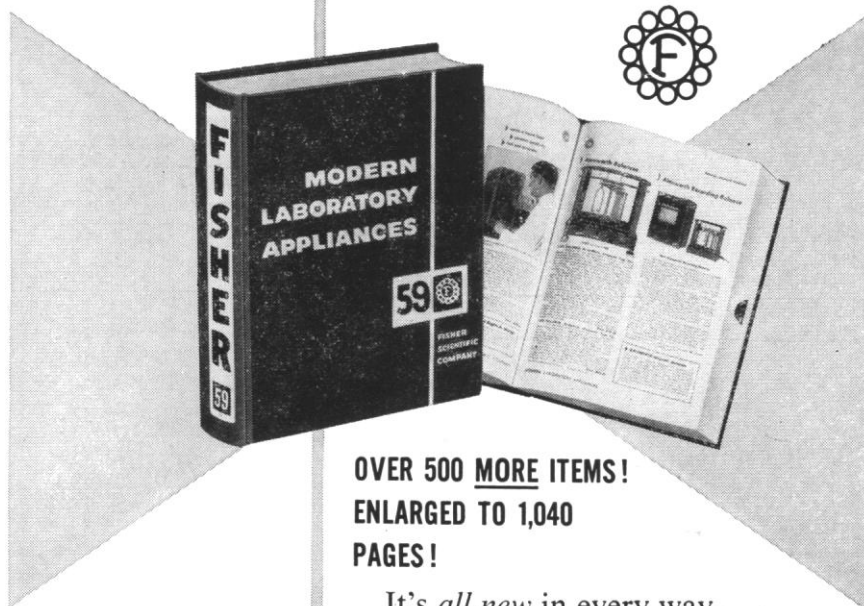
ing to F. Baclesse (Paris) has been improved to deliver an increased dose of radiation to the tumor. This is achieved by physical means, such as rotation, convergence, or grill therapy, and by biological means such as dose fractionation, and high voltage sources are valuable. For conventional x-ray therapy 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 Au¹⁹⁸ 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 carcinoma, 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 Au¹⁹⁸ 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

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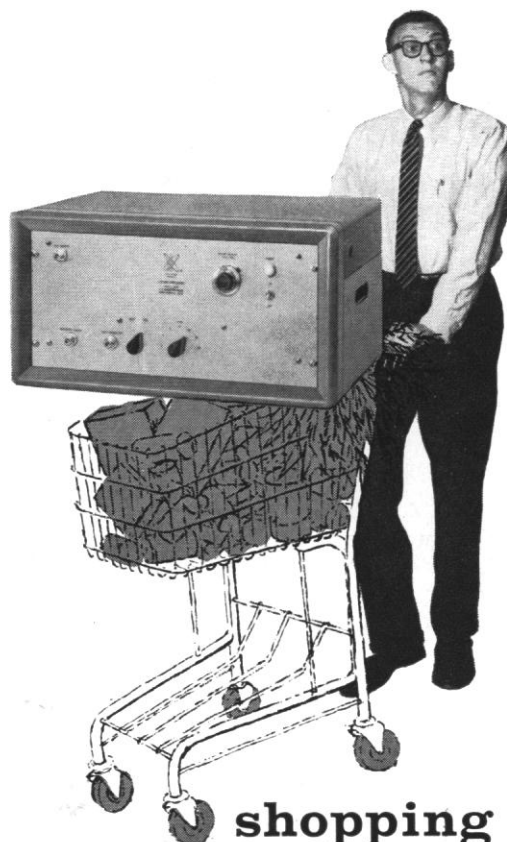
of female rats with a single dose of 5 mg of methylcholanthrene, given by stomach tube; both Shay and Huggins used such tumors to assay hormonal and therapeutic agents.

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 $\text{CH}_3\text{—N—}(\text{CH}_2\text{—CH}_2\text{—Cl})_2$, 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 non-functional ribonucleic acid molecule, while, according to P. Feigelson and J. E. Ultmann (New York), it also inter-



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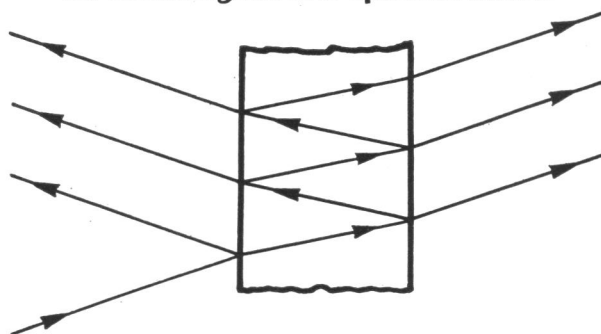
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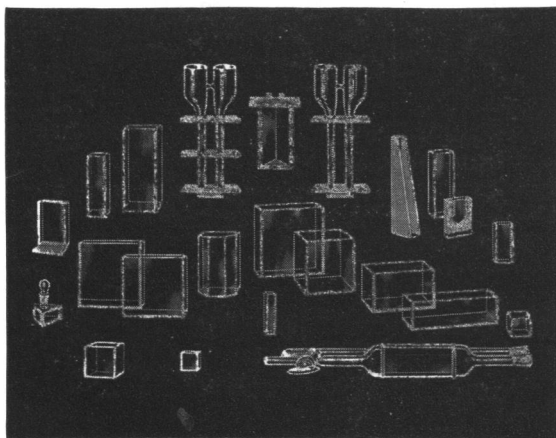
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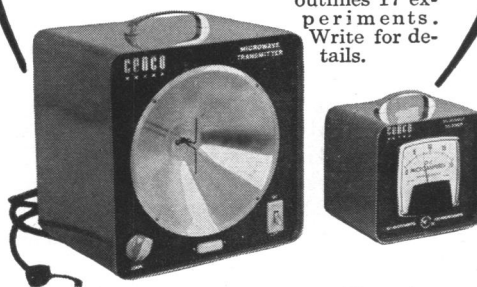
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feres with nucleic acid metabolism by in vivo inhibition of xanthine catabolism. Similarly, C. Heidelberger reported that 5-fluorouracil and related analogs form nonfunctional (or "fraudulent") nucleic acids and also inhibit nucleic acid biosynthesis. 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 ethyleneimino-quinone "E-39" inhibits cell glycolysis (N. Gerlich and H. J. Wolf, Bielefeld, Germany) and often gives satisfactory remissions in metastatic cancer and chronic lymphomatosis (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-

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