

particular process the series of contributions from the irreducible graphs diverges in an oscillatory manner with great rapidity. When the coupling constant is small, say $1/137$, successive terms decrease rapidly at first, but ultimately the enormous number of graphs becomes the predominant factor. In pseudoscalar π -meson theory the coupling constant may be in the range 4–40, and at no stage does the series even appear to converge.

During the discussion, Prof. Peierls pointed out that a weakness of the work is the lack of any estimate of the finite contributions from the self-energy and vertex parts occurring in the graphs.

The work of B. F. X. Touschek and of Dr. W. K. Burton on field equations and commutation rules was then described by the latter. Dr. Burton referred to a recent paper by J. Schwinger¹ which gives an account of a comprehensive scheme for the quantum mechanics of localizable fields based on an operator Lagrangian. The theory makes no appeal to the correspondence principle or an underlying classical theory, and all the results are derived from a single fundamental principle analogous to Hamilton's principle in classical theory. This theory has been shown by Burton² to lead to a particularly simple derivation of the S -matrix series in terms of the interaction Lagrangian. Schwinger describes how the commutation relations are to be obtained from the fundamental postulate; and, by studying examples from particle mechanics, Burton and Touschek found that the Schwinger method gives a unique prescription for the determination of the commutation rules for systems free from anholonomic constraints. If such constraints are present, the method may—in special cases—no longer apply as it stands. Equations of the Dirac type belong to this category, since the number of degrees of freedom is just half the number of co-ordinates appearing in the Lagrangian.

The final lecture, by Dr. J. S. R. Chisholm (Glasgow), dealt with the calculation of higher order S -matrix elements. Dr. Chisholm demonstrated explicitly automatic procedures for carrying out the calculations according to a prearranged programme. Previous efforts in this field appear as special cases of the general method which he detailed. Dr. Chisholm brought out clearly the principles described at length in his published work³. S. C. CURRAN

¹ *Phys. Rev.*, **82**, 914 (1951).

² *Phys. Rev.*, **64**, 158 (1951).

³ *Proc. Camb. Phil. Soc.*, **48**, 2, 300 (1951); and *Proc. Roy. Soc.* (in the press).

PROGRESS OF CANCER RESEARCH

THE reviewer of a production like the Annual Report of the British Empire Cancer Campaign*, which covers a wide field of research, will naturally tend to limit his choice of investigations for description to those with which he feels at home, or which seem to him to be especially interesting, original or promising. The subjective element in selection is unavoidable and, in fact, will become more pronounced as cancer research extends, since the range of studies as a whole is beyond the scope of any one reviewer.

Carr, in experiments on the virus of Rous sarcoma, has found that it is recoverable from the leg of a

British Empire Cancer Campaign 29th Report (1951). Edited by Sir Heneage Ogilvie (11 Grosvenor Crescent, London, S.W.1).

chick when the muscle is extracted a few hours after injection; after 6 hr. it can no longer be detected in any quantity, but at 66 hr. it can again be separated in amount greater than was injected. It is believed that the infective virus disintegrates into smaller components inside the cell, that these multiply and recombine to give the infective virus. "All these considerations lead to the suggestion that infective virus is present in the cell for only a very short proportion of the mitotic cycle. It therefore seems probable that the malignant condition is caused by some earlier stage of the virus multiplication cycle, and this leads to the possibility that a tumour may sometimes result from a non-infective virus."

Investigations at the Chester Beatty Institute on chromosome abnormalities induced in *Drosophila* by chemical mutagens (nitrogen mustards, diepoxides, ethyleneimines, dimesyloxyalkanes) have shown that these changes are observed as partial deficiencies. This fact has been used in support of a theory of malignancy, the outline of which can be sketched in as follows: (1) Many carcinogens are also potent inducers of mutations in *Drosophila*. (2) There must therefore be some fundamental relation between carcinogenesis and mutation (hence the somatic mutation theory of cancer). (3) Mutagens acting on *Drosophila* induce chromosomal abnormalities, namely, deficiencies and minute deletions. (4) It is possible, therefore, that cancerous transformation also is an expression of a chromosomal deficiency, that is, an interference with the reproduction of the gene pattern. (5) Hence the cancer cell is a normal cell which has irretrievably lost something clearly it has lost its growth-controlling mechanism. (6) The specific hormones control the growth of their target organs and xanthopterin brings about renal hypertrophy; therefore an obvious aim of cancer research must be to find a chemical compound or an enzyme which can replace the lost growth-controlling material of the malignant cell.

There exist some different types of chromosomal aberrations which are not permanent features of tumour tissue. In an account of the work of Koller and associates, it is stated: "From continued study of cytological abnormalities frequently observed in the cells of tumours induced by the aromatic nitrogen mustards it is clear that these are of 2 classes, those which gradually disappear in the course of serial transplantation, and those which continue to be transmitted to the descendant transplant generations, apparently indefinitely. Even these permanent abnormalities are, however, still regarded only as associated changes, and not in themselves the cause of the malignant alteration, which can clearly occur in their absence. They are nevertheless of great interest as suggesting a likely site of action of these carcinogens, and it is probable that the malignant transformation itself involves a much less tangible or even 'invisible' effect on the chromosome or gene".

Ludford, who has been studying variations in size and structure of the malignant cells of transplantable tumours in inbred strains of mice, says: "On the basis of these observations it seems justifiable to conclude that cellular polymorphism correlated with variations in chromosome numbers and aberrations of the process of mitosis are not specific features of malignancy but occur, although to a lesser extent, in normal tissues. This suggests the probability that after cells have become differentiated the full chromosome complement is no longer essential for their continued life and functional activity".

Cancer of the bladder in dye and rubber workers, and skin cancer due to mineral oils in the engineering industry, have been the subject of investigation by Case and by Woodhouse and Hieger. Case, in a statistical examination of bladder cancer, finds that the great increase of this disease between 1901 and 1950 cannot be entirely attributed to an ageing population, nor to improvements in diagnostic method. The occupational study of the rubber industry shows that a hazard is located in the mixing, extruding and vulcanizing sections of the industry, and that the risk was introduced between 1915 and 1930. This date would be compatible with the time when carbon black, some organic accelerators and anti-oxidants first began to be used on a large scale.

The biological testing of fractions of petroleum oils from different sources has as its objects the identification of the active agent in the oils and the development of a technique for assessing the industrial risk attached to the use of any one particular oil. Fractions of petroleum from oil-fields in the Middle East, Venezuela and the United States were prepared by distillation under conditions in which cracking was avoided in order to preserve the composition of the oil as nearly as possible in its original state. These fractions when tested by an elaborately designed series of experiments on mouse and rabbit skin showed pronounced differences of activity; they were much more carcinogenic for rabbit skin than for mouse skin—a further example of the unpredictable differences of susceptibility of different tissues and species to carcinogens.

Doll has conducted an inquiry into factors which may affect liability to cancer of the cervix uteri. It has been shown by a large volume of data that Jewish women have a lower incidence than Gentile women and that child-bearing is conducive to this form of cancer. Gagnon has now produced some unique evidence on this question. In the medical records of a population of nuns (annual average 3,280) in Quebec for the past twenty years, no case of cancer of the cervix was found. Inquiry is being made as to whether a similar investigation could be made in any other country (for example, Bavaria).

Sir Ernest Kennaway and collaborators have carried out an intensive examination of lung cancer, particularly from statistical material and by a study of carcinogens in the atmosphere and in tobacco smoke. Although it is now highly probable that cigarette smoking is an important factor in the very rapid increase in lung cancer in the past few decades, many other problems of lung cancer remain at present unexplained. For example, cancer of the larynx has shown no equivalent increase during this time. In Norway and in Mexico, cancer of the lung is about as frequent in men as in women; in England it is much more common in men; deaths attributed to cancer of the lung in both sexes and to cancer of the larynx in males are higher in the more urban districts, while in women the relation is reversed. The role of the geographical factor in differences of incidence of cancer presents some attractive problems. "The peculiar position of Wales in relation to cancer was first observed by Stocks (1930), who discovered the high incidence of cancer of the stomach in the north-western counties of Wales"

Gwyn and Salaman, in experiments on co-carcinogenesis, have found that if the skin of a mouse is given a single painting with 9:10-dimethyl-1:2-benzanthracene, followed after an interval of six weeks by treatment with co-carcinogen (croton oil in

paraffin oil), the rate of appearance and yield of tumours suggests: (1) that there is a critical size for tumours produced by this method which is rather less than that of the smallest visible; tumours smaller than this do not continue to grow—in fact, regress—if co-carcinogenic treatment is stopped; (2) the change produced by croton oil in mouse skin previously painted with a carcinogen is a gradual one; it is reversible during the greater part of its course, but becomes irreversible and independently progressive not long before the appearance of a visible tumour.

At Leeds, Dmochowski and co-workers have continued their researches on the Bittner milk factor. Electron microscope photographs show that in human milk, and in extracts of human breast tumours, especially from pregnant women, there exist particles of a size approximately the same as the Bittner agent. The virus is not antigenic in mice, and the antibodies elicited in mice react with extracts of mouse tumours whether or not they contain the agent as well as with different normal mouse tissues. No evidence could be found of a common antigen in human and mouse tumour extracts. Electrophoretic estimations show that the infective dose of the milk agent is extraordinarily low, namely, 3×10^{-7} μg m. of nitrogen.

Dmochowski finds that after eighty-six successive transplantations of the mammary tumour, the milk factor can no longer be detected, although there is no histological difference between the tumour at its eighty-sixth and forty-second passage. Apparently the presence of the milk factor is not a permanent feature of this transplantable tumour, and the cells can continue to multiply even when the agent cannot be detected by the technique employed. A similar disappearance of the virus from the transplantable Shope rabbit carcinoma has been described by workers in the United States. Dmochowski refers also to experiments demonstrating the appearance of the milk factor *de novo*, as reported in studies by Bittner.

Bonser and Jull have used a new method of testing carcinogens on the bladder by introducing the compound as a suspension in a paraffin wax pellet directly into the dome of the bladder of the mouse. Epithelial changes starting with hyperplasia and squamous metaplasia, and going on to benign and malignant hyperplasia, resulted from the introduction into the bladder of 20-methylcholanthrene, 2-amino-naphthol, and 3:4:5:6-dibenzcarbazole. Claysen reports that a relationship exists between species susceptibility to the carcinogenic action of 2-naphthylamine and the proportion of this compound which is excreted as 2-aminol-1 naphthol conjugates. Moreover, since 2-amino-1-naphthol is also carcinogenic when injected subcutaneously, the suggestion is put forward that in carcinogenesis by 2-naphthylamine the amine has first to be converted to the naphthol.

At the Sheffield centre, strenuous efforts have been made to induce stomach cancer in rabbits, rats and mice by injecting rapidly-acting carcinogens into stomach fistulæ, by feeding hot food at 55° C, by administration of 2-acetyl-aminofluorene or methylcholanthrene with croton oil by mouth, by exhaustion of the mucosal secretion with dodecyl sulphate or with 50 per cent ethanol followed by 9:10-dimethyl-1:2-benzanthracene in the drinking water. The results were negative. "All the available evidence still suggests that the stomach is refractory to chemical carcinogenesis because of its powerful mucous

barrier. Perhaps the main value of all this work is that it suggests that the inducing agent in stomach cancer is not an extrinsic chemical carcinogen."

Pybus and Miller, at Newcastle, have carried out experiments somewhat on the lines of Strong's method, namely, the injection of mice with methylcholanthrene for a number of generations to see if subsequent generations will contain mutations observed as spontaneous neoplasms without the necessity of applying carcinogens.

Lasnitzki at Cambridge has confirmed Craigie's report that mouse sarcoma 37 consists of at least two types of cells, the more active variety (round cells refractile in phase contrast) being convertible *in vivo* and *in vitro* into the more differentiated spindle cells.

Peacock has reported that hybrid mice from *CBA* strain (virus-free) mothers and *C₃H* (virus-bearing) fathers can acquire the virus if the father remains in the breeding box during pregnancy and the puerperium. If the *CBA* mother is transferred to a sterile breeding box early in pregnancy and remains segregated until the litter is weaned, the female hybrids show no greater incidence of mammary cancer than pure line *CBA* females.

Peacock has been more successful than the Sheffield workers in inducing stomach tumours in mice; he used feeding with carcinogens and with cottonseed oil heated to 350° for some hours. In an experiment in which the oil was fed for 300 days in a series of mice of which 230 lived more than 400 days, fifteen cases of papilloma and six of squamous carcinoma or adenocarcinoma of the forestomach and adjacent glandular stomach and three cases of adenosis of the pylorus were found. "Thus it seems probable that the 21 cases of tumour of the forestomach among 230 mice fed with heated cottonseed oil were directly related to this treatment. Though a 10 per cent yield is small compared with many experimental results, it is at least as high as the incidence of cancer of the stomach in the human subject." However, the stomach tumours evoked in the mouse are rather different from human gastric cancer, and Peacock suggests that this difference is due to the occurrence of gastritis, pernicious anaemia and achlorhydria, which is common in man but rare in animals.

The fundamental problems of dosimetry are still receiving a large amount of attention in practically every centre concerned with treatment by any form of radiation. Methods of measurement vary from the proportion of survivals of the broad bean root to the reduction of ceric sulphate. The use of photographic nuclear research emulsion for fast-neutron dosimetry is also being compared with the more usual method of using an ionization chamber with walls of a gelatin mixture. Depth-dose measurements vary from those made on a 30-MeV. beam in a water phantom, to beta-rays using a stack of films as phantom. The protection of workers in these fields is also being continually studied. In a number of departments a film badge service is provided, and one report discusses the method of determining the energy of scattered rays by means of secondary electronic emission from metal foils. Reports from two centres using a 30-MeV. synchrotron indicate that while treatment is tedious owing to the low output of 9-10 r./min. at 1 metre, yet useful information is being gleaned about the distribution of the dose in tissue. The few patients who have been treated have shown encouraging results.

Numerous reports indicate the ever-increasing use of radioactive isotopes as a tool for research as well

as for diagnosis and therapy. Considerable strides have been made in the design and operation of scintillation counters, and reports from a number of centres indicate that the increased sensitivity of this means of detecting radiation should lend itself to a much more efficient study of radioactive material in the body. A 4π scintillation counter for the absolute standardization of radioactive isotopes is also reported. The importance of absolute standardization, particularly of radioactive isotopes in frequent use, has been realized, and work is going on in several centres to attempt to reach agreement on this point. There is an increasing demand for discrete sources of radiations, and work is reported on surface applicators, using the gamma radiations from gold-198, which is spread over a 'Perspex' or polythene mould in the form of gold foil of varying thickness, and the entire unit then irradiated at the Atomic Energy Research Establishment. Cobalt-60 is now used as a central source in the intracavitary treatment of carcinoma of the bladder and also in the treatment of carcinoma of the cervix. Superficial beta-ray applicators using phosphorus-32 (as red phosphorus) incorporated into plastics are also giving encouraging early results. The installation of two cobalt-60 beam-therapy units using up to 1,400 Curies of cobalt-60 is reported from Canada (see also *Nature*, 168, 1035; 1951)

The clinical and pathological reports consist chiefly of the continuation of orthodox analyses of malignancy at various sites with correlations including stage, histology and response to treatment. The findings confirm the value of histological grading in assessing prognosis. Similar investigations are being carried out independently at a number of centres in Great Britain, but there is little evidence of any co-operative planning. The most detailed survey reported is on seventy-four cases of nephroblastoma from the Hospital for Sick Children.

At the Chester Beatty Institute it is found that 1:4-dimethanesulphoxybutane given in long courses of small doses has proved capable of producing remissions of therapeutic value in myeloid leukaemia. At both the Westminster and the Christie Hospitals it has been found that the nitrogen mustards are useful in the treatment of advanced Hodgkin's disease.

Glücksman and his colleagues are studying the mechanism of lymph-node involvement and the reaction of the node to the presence of tumour in cancer of the cervix. They have also accumulated impressive results on the value of the cytological analysis of serial biopsies in the assessment of the radiocurability of cancer.

Cuthbert Dukes has confirmed the frequent development of cancer of the large bowel in long-standing cases of ulcerative colitis. He and his colleagues have found that precautions recently adopted to prevent implantation of cancer cells during the operation of restorative resection for cancer of the rectosigmoid have indeed prevented the recurrences at the suture line which were met with formerly.

Price, at Bristol, in an analysis of thirty-six cases of osteogenic sarcoma, found the mitotic ratio (the number of resulting nuclei to one in mitosis) to be the most reliable index of malignancy. A mean mitotic ratio of 238 to 1 was obtained for the whole series, based upon an examination of at least 2,500 nuclei for each count. The tumours were divided into three grades of malignancy on the basis of the

mitotic ratio. These showed good correlation with the time of survival of the patients in months from the date of the presenting symptom. The conclusions are most promising, but it would appear that the number of mitotic cells counted, especially in the 'low-grade' malignancies, must have been extremely small. His published article on this work does not give the actual number of mitotic cells counted and therefore does not dispel statistical doubts about the method as it stands.

PHYSICAL CHEMISTRY OF PROTEINS

A GENERAL discussion on "The Physical Chemistry of Proteins" was held by the Faraday Society in the Department of Zoology, University of Cambridge, during August 6-8. During the meeting, introduced by Dr. J. T. Edsall of Harvard University delivering the sixth Spiers Memorial Lecture, some twenty-five papers, a large proportion by foreign authors, were presented.

The programme was divided into five sections arranged in order of increasing complexity: (1) experimental techniques, (2) low molecular weight proteins, (3) high molecular weight systems, (4) protein interactions, (5) conjugated proteins. An audience of 350-400, containing many guests from abroad, attended.

Dr. Edsall, a Fulbright Fellow of the University of Cambridge, began by reviewing the fundamental changes in our ideas on proteins since the middle twenties, when little quantitative information was available. Subsequent years saw the development of the ultracentrifuge and other physical methods by which information on the size and shape of many proteins has been obtained. Among recent developments, Dr. Edsall mentioned particularly the work of Sanger and co-workers, which has provided very complete information on the sequence of amino-acids in insulin, and the structural suggestions of Pauling, Corey and co-workers. Illustrating the state of our knowledge of the physical chemistry of proteins, Dr. Edsall dealt in detail with two important proteins—fibrinogen and serum albumin. There was general agreement that fibrinogen is an asymmetric molecule of molecular weight *c.* 400,000, but many more detailed questions and the mechanism of blood clotting require further study.

Serum albumin is one of the most-studied proteins. The molecular weight was thought to be *c.* 69,000 until very recently, when new experimental work has indicated that a somewhat lower value may be correct. As to the shape of the molecule, the greater part of the data is in accord with an ellipsoid of rotation of low axial ratio; details remain to be settled. While the molecule is supposed to be relatively rigid in solution, it is possible that some flexibility of the surface exists; such a property would go far towards explaining the ability of the molecule to combine with a large variety of organic and inorganic materials. Dr. Edsall considered in detail the binding of zinc and mercury atoms.

In section 1, only the more recent advances in experimental techniques were considered. In a paper by A. Tiselius, zone electrophoresis in filter paper and other media was reviewed. Since separate bands are thus produced, the method has distinct advantages over boundary electrophoresis as a prepara-

tive tool. It can readily be operated on a micro scale, at low concentrations and for a variety of materials of low molecular weight as well as macromolecules. On the other hand, electro-osmosis and adsorption may hamper quantitative work, and special measures are necessary if such effects are to be avoided. G. Weber presented a paper on the use of measurements of the polarization of fluorescence in investigating proteins in solution. Results on several protein preparations were quoted, among which those on bovine serum albumin, indicating reversible dissociation at low salt concentration and acid pH's, were of especial interest. Variation of the protein concentration causes no apparent effect on the dissociation. Confirmation of these results was reported from osmotic pressure and sedimentation-diffusion studies. Several workers, however, were doubtful about this interpretation, attributing the apparent dissociation to effects of the high positive charge of the molecule under the conditions of the experiments. A final paper in this section, by J. S. Falconer, D. J. Jenden and D. B. Taylor, dealt with the application of solubility measurements to the study of complex protein solutions and to the isolation of individual proteins. In illustration, the fractionation of rat liver was considered.

The section on low molecular weight proteins began with a paper by P. Doty and G. E. Myers dealing with the thermodynamics of the association of insulin. Light-scattering measurements at acid pH's and varying salt concentration were used to evaluate the constants governing the equilibria between monomer, dimer and trimer over the range 20°-40° C. From discussion of the molecular weight of the insulin monomer, it would appear that the bulk of the kinetic data now supports the value 12,000. In a paper by H. Neurath and co-workers, the kinetic behaviour of trypsin and related molecules was considered. When trypsin is examined under conditions favourable to enzymatic activity, the sedimentation constant, varying with the age and pH of the protein solution, corresponds with autolysis of the protein. On the other hand, when the enzyme is stable and inactive, no such anomalies are observed. Trypsinogen and the diisopropylfluorophosphate derivative similarly show normal behaviour. A molecular weight of 24,000 was reported for the inactive proteins. G. E. Perlmann presented an electrophoretic study of enzymatically modified ovalbumin and casein. The reactions considered were: (1) the ovalbumin-plakalbumin transformation in which carboxyl groups are liberated, and (2) the dephosphorylation of ovalbumin, plakalbumin and casein. In each case, characteristic changes in electrophoretic mobilities and patterns were produced; electrophoresis is thus a useful tool in following enzyme changes involving charged groups. E. Barbu and M. Joly dealt with the transformation of certain globular into fibrous proteins by moderate heating, salt effect, or high pressure. Several physical methods were utilized, and the authors suggested that end-to-end aggregation rather than unfolding of the molecules is responsible for the fibrous products obtained. Denaturation was treated in the light of the results obtained. In the following discussion, several workers directed attention to denaturation reactions which would be difficult to explain by end-to-end aggregation and for which chain unfolding is the more likely explanation.

In section 3, the first paper, by P. Johnson and W. E. F. Naismith, reported experimental results