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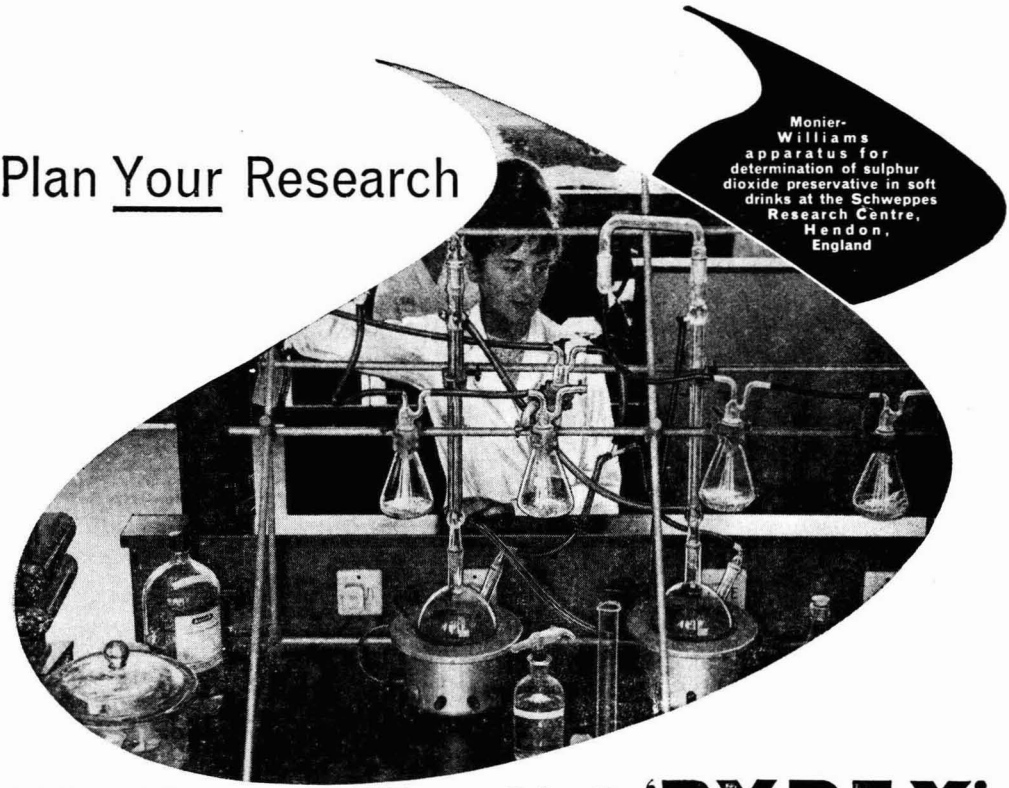

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Current Topics

International Cooperation in Cell Biology

THE International Cell Research Organization (ICRO), founded in 1962 under the auspices of Unesco, has set upon itself the task of establishing new forms of cooperation among laboratories scattered throughout the world. The organization seeks to impress upon the governments of different countries the need for stepping up basic research in cell biology as work in this field would greatly add to our understanding of the processes underlying genetic diseases, metabolic disorders and cancer.

Scientists are finding it increasingly difficult to keep up with research in their own specialized fields and with the advances being made in life processes in general. This is a result of the accelerated pace of discovery in the life sciences, the ever-growing number of new publications coming out each year, the constant development of new techniques and the increasing use of the methods of modern physics. It takes a year or two for the results of a crucial scientific experiment to find their way into a periodical available for consultation in libraries of universities and research institutions. And it may be five or ten years before a book is published summing up in assimilable form the pioneering advances made by a scientist.

In the United States, scientific information is disseminated with a speed commensurate with the pace of scientific progress. This is possible because of the large number of laboratories covering the entire country and because of the opportunities for American scientists to obtain travel grants — not to mention the use of the long-distance telephone between different cities or areas. But nearly everywhere else research workers usually have only sporadic contacts with their colleagues abroad, or even in their own countries. In more than one laboratory, a scientist runs the risk of being outdistanced by others if he tackles a problem of major interest. And he often gives in to the temptation of devoting himself to questions of less importance, thus avoiding the danger of competition from better equipped laboratories.

The ICRO Council fully realizing that any externally imposed attempt at guidance or coordination, or any effort to assign research roles, is doomed to failure, felt that much could be done to increase contacts among scientists so as to keep them abreast of current work and to help provide research workers with the equipment they need, and perhaps also to make it possible for them to use the facilities offered by other laboratories. In this way, it would be possible to give each scientist an opportunity to do his best and contribute to a task that is collective by its very nature.

As a first step in this direction, six research centres have agreed, at the suggestion of ICRO, to form a sort of federated network. Meetings will be held at each centre in rotation to discuss common problems and to set up a programme of cooperative research. These laboratories, located in Edinburgh, Naples, New York, Paris, Prague and Rehovoth (Israel), are all centres of intense scientific activity largely because their research groups represent a variety of different scientific disciplines. It is expected that this network, set up as a pilot project, will be expanded in the near future. The experience provided by this venture in cooperative scientific endeavour should also be of value to other networks of the same type planned for a later date. In this way, international cooperation in science will take on a more concrete form. At the same time, it was felt that, in addition to cooperation among groups of laboratories, a programme should be established providing for individual exchanges to enable research workers to spend periods ranging from three months to two years in foreign laboratories. For the successful implementation of a plan of this kind, two conditions need to be met: first, a considerable increase in available resources, primarily through the establishment of a substantially endowed international fund; and, secondly, the compilation of a list of all cell research centres accompanied by a summary of their activities and information on their equipment and facilities for accommodating foreign scientists. ICRO is drawing up such an inventory and hopes to have it completed in two years.

ICRO also arranges for intensive refresher courses on subjects in which new work has been quickly accumulating. A major reason for initiating these courses is the desire to promote the interaction of different scientific disciplines. In this connection it has been noted that nuclear physicists who turned to molecular biology have made spectacular scientific contributions. The courses are designed primarily for research workers who have already made a mark in a given branch of biology or physics. Two courses were offered in 1963; one in Naples on bacteriophages and the other in Leiden on modern techniques of tissue culture. Young scientists from 12 countries attended these courses. During 1964 an embryology course is to be held in Naples in April, and a course on the interaction of animal viruses and host cells from 6 April to 2 May at Bratislava, in Czechoslovakia. In the autumn, the Naples course on bacteriophages is to be repeated.

In December 1964, a group of biologists from Europe, UK, USA and Asia will visit India and for a week meet and hold discussions with Indian biologists. The visit of this international group of biologists is particularly opportune as the Council of Scientific & Industrial Research is actively engaged

in drawing up the blue prints for the proposed National Biological Laboratory. This laboratory may well become the first research centre in the South East Asia region to join the network of research centres and take an active part and make useful contribution to the cooperative research programmes initiated by ICRO. Such a step will go a long way in ensuring the progress of biological research in the country on proper lines.

Indian Programme of Space Research by Sounding Rockets

THE successful test launching into the upper atmosphere of the first Indian research rocket on 21 November 1963 marked the modest beginning of India's space research programme. Though assistance from a number of nations, chiefly USA, USSR and France, in the form of supply of scientific equipment, initial planning and training in technical know-how, was received, the operational part of the launching was handled entirely by Indian scientists and engineers. The rocket was fired from the rocket launching facility established at Thumba (near Trivandrum) in Kerala State. Since the firing of the first rocket, a series of launchings were undertaken as planned and completed to schedule.

Location of the rocket range site at Thumba was decided upon mainly because of the special scientific interest the site offers. The rocket range will serve as an international facility for teaching, training and research and it is suggested that the centre be administered by the UN Committee for the Peaceful Uses of Outer Space.

The unique advantages afforded by the Thumba rocket site arise from (1) its strategic location almost exactly on the earth's magnetic equator and (2) the fact that the strength of the magnetic field in India is the highest that is reached anywhere on the geomagnetic equator. These two factors make the site ideally suited for investigations in problems in meteorology and the atmospheric sciences peculiar to both geographic and geomagnetic equatorial regions. The Indian national programme of rocket research comprises launching of (1) rockets with sodium vapour payload, (2) rockets with magnetometer payload and (3) meteorological sounding rockets.

The first rocket fired from Thumba on 21 November 1963 was of the sodium vapour payload type. It was followed by two more launchings on 8 and 12 January 1964. The rockets used for this series of launchings are of GSFC Nike-Apache type which are unguided two-stage rockets (length, over 320 in.; diam.: Nike rocket, 16·5 in. and Apache rocket, 6·5 in.; payload, 70 lb.) fired at an angle of 80° (and azimuth 235°). The first stage of the rocket (Nike) burns out in about 3·5 sec. after launching and drops into the sea; the second stage rocket (Apache) takes the payload up to *c.* 180 km., attaining a maximum speed of 3840 km./hr. The sodium vapour payload releases a bright orange-coloured vapour cloud into the sky from an altitude of 80 to 180 km. The rocket is fired during twilight when the sodium vapour is lit by the sun's rays, which do not fall on the surface of the earth but reach only the upper atmosphere; the experiment could also be conducted at dawn. The brilliant vapour cloud visible as far as 250 km. away is photographed by special cameras installed at a number of ground stations, viz. Kanyakumari, Palayamkottai, Kodaikanal and Kottayam. By correlating the information from these stations where the cloud is photographed against the background of stars, it is possible to gain fresh insight into a number of problems connected with the electrojet and high altitude aeronomy in the Indian Ocean area.

The series of launchings with magnetometer payload, using the same type of two-stage rockets, began on 25 January 1964 and carried special instrumentation to telemeter, during flight, signals connected with magnetic elements. This series of experiments is intended to measure the magnetic fields caused by the currents in the electrojet and the temperature and charged particle densities in the ionosphere. The tracking of the rockets and the reception of the telemetred signals from the rockets (using computer data processing techniques) also form an important part of this programme.

Meteorological sounding rocket programme, commencing in March or April 1964, will be carried out by small rockets of the Judi-Dart class, carrying instruments (up to 10 kg.) up to a height of 70 km. The experiments conducted with these rockets are mainly intended for obtaining a better understanding of the meteorological parameters such as temperature, winds and composition of the lower atmosphere which determine weather. The data collected from this series of experiments are expected to be of interest and use in the programme chalked out by the India Meteorological Department during the International Indian Ocean Expedition and will also be of value in the International Quiet Sun Year programme which commenced from 1 January 1964.

The success of these launchings (the one launched on 8 January 1964 went right through the electrojet as expected) is ample testimony to the skill and ability of the Indian scientists and engineers in tackling the innumerable problems which require innovation of indigenous equipment on the site. The completion of the proposed Space Technology Laboratory at Trivandrum may be expected to give an added fillip to the pace of Indian space research from these modest beginnings.

International Conference on Cosmic Rays

R. P. KANE
Physical Research Laboratory, Ahmedabad

UNDER the auspices of the Cosmic Ray Commission of the International Union of Pure & Applied Physics, the Eighth International Conference on Cosmic Rays was held at Jaipur during 2-14 December 1963. This conference is held once every two years. The last one was held at Kyoto, Japan, in September 1961.

The Jaipur conference was held at the invitation of the Department of Atomic Energy of the Government of India and was formally inaugurated by Prof. H. J. Bhabha, Chairman of the Indian Atomic Energy Commission. The inaugural function, held on 2 December 1963, was presided over by Prof. P. M. S. Blackett (UK) and the conference began with welcome speeches by Prof. M. G. K. Menon and Prof. V. A. Sarabhai and opening remarks by Prof. Bhabha and Prof. C. F. Powell.

Extensive Air Showers

The opening session on 2 December was devoted completely to Extensive Air Showers in Cosmic Rays and consisted of introductory talks and reviews of work carried out by leading research groups in the world. Dr V. Domingo spoke about the scientific activities at Mt Chacaltaya in Bolivia, South America, the highest research laboratory in the world (altitude 17,000 ft). This was followed by a talk by Dr K. Suga about the work on Extensive Air Showers at the same place. Prof. J. G. Wilson and Prof. C. B. A. McCusker described the air shower projects at Haverah Park, UK, and Sydney, Australia, respectively. On each of the succeeding working days, there were two sessions in the morning and two in the afternoon.

The morning session on 3 December was devoted to communications pertaining to Extensive Air Showers. Apart from the interesting group reports of Dr M. Oda about work at Tokyo and Dr B. V. Sreekantan about work at the Tata Institute for Fundamental Research (TIFR), Bombay, several workers reported on detailed characteristics of Extensive Air Showers and the conclusions regarding the energy spectrum and composition of the primary particles responsible for the initiation of air showers. The Australian group reported that there was no unique structure function which would describe all cores, which can be classed as single, multiple or flat topped. For the single cores, the Nishimura-Kamata function holds to within 20 cm. of the core. The multiple cored showers cannot, however, be easily explained as due to several pi-zero mesons produced in a single process. It looks as if singly cored showers are due to proton primaries, whereas multiple cored or flat topped ones are due to heavier primaries. For energies $> 10^{15}$ eV., the proportion of the latter increases significantly, indicating probably a change of composition above this energy. It was also concluded that there was no violent change in the characteristics of nuclear interactions in this energy range. The MIT Volcano Ranch Station experiment gave another interesting result, viz. that in the integral energy spectrum of the primaries, there is evidence for an inflection occurring somewhere between 10^{15} and 10^{17} eV.[1] This indicated an extra flux of very high energy particles and was interpreted as a possible crossover between galactic and metagalactic cosmic rays, an exciting possibility. Several workers, particularly the TIFR group and the Moscow University group, reported detailed information about the lateral distribution of the various components in the air showers. Evidence was presented to show that the total number as well as the lateral distribution of both N and mu component fluctuate from shower to shower and that there are rather interesting correlations between the lateral distributions of the electron, muon and N components. Further evidence for a very small ($\frac{1}{2}$ per cent) but statistically significant proportion of photonic Extensive Air Showers in the total Extensive Air Showers was also presented.

It is realized now that the problem of Extensive Air Showers cannot be studied fruitfully unless all the components are studied simultaneously. In particular, the muon content of Extensive Air Showers has become very important as showers rich in muons are attributed mainly to heavy primaries, while those having low muon content are possibly initiated by gamma rays. Different groups described complex experimental arrangements to enable such a study to be carried out in great detail and it is hoped that in the next few years, these would yield very valuable details of the Extensive Air Shower phenomenon.

Extensive Air Shower arrays can also be used for studying the arrival directions of the showers. The afternoon session on 3 December was devoted partly to discussions on this aspect, the participants being mostly Japanese workers. Some evidence was presented to indicate possible anisotropies in the side of the spiral out of the galactic arm and that these were heavy primaries. A search for high energy gamma ray sources has proved fruitless. Experiments conducted by the British group also indicated negligible anisotropies in air showers.

Composition and Intensity Variation of Cosmic Ray Primaries

The problem of primary electrons and photons in cosmic ray intensity is of considerable interest as the presence of electrons and photons in the primary radiation is expected to throw light not only on the various processes occurring in interstellar space but also on the problem of origin of cosmic rays itself. As remarked by Dr Hayakawa of Tokyo, several theoretical models predict an

appreciable flux of such radiation and it was such optimistic estimates which stimulated a number of experimenters to design apparatus for the detection of these radiations. Results obtained by several leading groups with satellites and balloon flights were reported. Most of these results indicated very small gamma ray fluxes. Regarding electrons, the primary flux still seems to be less than 1 per cent and among these, electrons far outnumber positrons. Several workers described proposed experimental set-ups for further work in this direction, whereas several others presented calculations about estimated fluxes from various astronomical sources.

Discussions at the afternoon session on 4 December were on the composition (heavy nuclei) of primary cosmic rays. The results of several studies pertaining to the fluxes of protons, alpha particles and heavier nuclei measured with balloon flights as well as satellites were reported. These studies have provided estimates of the fluxes of the various components with statistical accuracies better than those obtained in the past. Some workers presented comparative values of the fluxes for different phases of the solar cycle. Comparison of results obtained by balloons and satellites has given an estimate of the albedo effect suffered by the balloon experiments. The evening session ran parallel to the Extensive Air Shower session where papers dealing with detailed properties of air showers were read.

The early morning session on 5 December dealt with the isotopic abundances in the primary cosmic radiation. The problem is intimately connected with the age of cosmic rays, their origin and their transformations in space. The relative abundances of He^3 and He^4, C^{12} and C^{13}, etc., therefore, assume a special significance. Refined experimental techniques for such estimations as also the results obtained by various workers were presented. The studies have indicated that the composition of primary cosmic radiation is energy dependent. The various isotopic abundances seem to be consistent with the amount of matter traversed by cosmic radiation before reaching earth equivalent to *c.* 5 g./cm.^{2}. Conclusions regarding possible estimates of the lifetime of this radiation as also the gas densities through which cosmic rays spend most of their time have also been drawn. Evidence was presented to indicate a possible supernova origin of cosmic rays.

Origin of Cosmic Rays

The rest of the session on 5 December was devoted to a discussion of the problem of the origin of cosmic rays. Dr B. Burbridge gave a detailed account of the possible extragalactic sources. A paper by Dr V. L. Ginsburg and Dr S. I. Syrovatsky examined in detail various locations in space for the origin of cosmic rays. Arguments were given to rule out the metagalactic origin theory except perhaps for cosmic rays of superhigh (10^{17} eV.) energies, and to support the theory of galactic origin of cosmic rays. Several workers discussed the possibilities of origin in sources like supernova. It was also pointed out that even the nuclei of ordinary galaxies could be powerful sources of cosmic radiation.

The conference proceedings on 6 December started with review talks by Dr G. Swarup on Radio Astronomy and by Dr K. R. Ramanathan on Solar Activity and Ionospheric Phenomena. Both speakers gave excellent accounts of the present status and situation in the two fields. The next item discussed was solar particle radiation. Excellent reviews were presented by Dr S. Biswas on Composition of Solar Particle Radiation, by Dr F. B. Mcdonald (read by Dr T. L. Cline) on Solar Particle Studies with Satellites, by Dr K. McCracken on Solar Particle Radiation and by Dr D. Lal on Radioactivity Induced by Solar Particles. These were followed by papers by various workers on the energy and charge spectrum of solar particle radiation. Measurements with precision better than that achieved ever before were described. Individual events connected with solar flares were also discussed. A study of the composition of solar radiation reveals that it is roughly the same as the natural abundance in Sun or similar ordinary stars. As this is in great contrast with abundances in galactic cosmic rays, it follows that Sun or similar ordinary stars cannot be the sole source of ordinary cosmic rays. The solar particle radiation also seems to have traversed an amount of matter less than *c.* 0·2 g./cm.^{2}. As density in interplanetary space is very small, this must be mostly at flare site. The basic facts emerging about the propagation of solar particle radiation are: (a) high energy particles are biassed towards the western limb of the Sun and low energy ones towards the centre; (b) some particles manage to reach the earth very rapidly while the majority seem to arrive by a sort of diffusion process; (c) very few flare effects are attributable to flares on back side of the Sun; and (d) mechanism responsible for Forbush decreases seems to be capable of trapping solar cosmic rays. Models capable of explaining these facts were discussed. In the late evening session, the aspect of Modulation was introduced. The session dealt mostly with measurement of intensities of various components at various altitudes and latitudes by balloons and satellites.

On 7 December, the conference opened with sessions on Interplanetary Plasma. After an illuminating talk by Dr E. N. Parker on the Theory of Solar Wind, a number of workers reported experimental observations relating to plasma and solar wind. Theoretical calculations about the interaction of solar wind with earth's magnetosphere and the propagation of shock waves in interplanetary plasma were presented and discussed. Evidence was presented to show correlated changes between solar wind velocities and geomagnetic, solar and cosmic ray activity. The afternoon session was devoted to Modulation where short-term effects like cosmic ray storms were presented and discussed and to a parallel session on Techniques where instruments like spark chambers and scintillation counters were discussed.

The late evening session was devoted to a general discussion about the week's proceedings. After competent reviews by Dr Zatsepin on Extensive Air Showers, by Dr M. M. Shapiro on Composition of Primary Radiation and by Dr B. Peters on Origin

of Cosmic Radiation, plans for future experimentation in these fields were discussed.

Modulation of Cosmic Rays

On 9 December, the conference continued discussions on different aspects of Modulation. After excellent reviews by Dr L. I. Dorman (read by Dr E. L. Feinberg) on Cosmic Ray Variations and by Dr V. A. Sarabhai on Modulation of Galactic Cosmic Rays, several workers discussed the long-term changes in the energy spectrum of primary cosmic rays. In the afternoon, Dr P. J. Kellogg and Dr A. Chudkov gave review talks on Radiation Belts. It was reported that not much progress was made in this field during the last 2 years. In the evening session on Modulation, group accounts were given by Dr A. G. Fenton (Australia), Dr Y. Sekido (Japan), Dr J. G. Roederer (South America) and Dr A. E. Sandstrom (Sweden) about their respective works in the field of Modulation.

Isotopic Studies

The proceedings on 10 December opened with a session on Cosmic Ray History based on isotope studies. After introductory remarks by Dr J. R. Arnold and an extensive and excellent review by Dr J. Geiss on the history of cosmic radiation as revealed by the study of isotopic composition in meteorites, several workers reported experimental findings pertaining to this subject. The study of the isotopic composition in meteorites, polar ice, ocean sediments and perhaps samples of lunar surface can yield valuable information on the history of cosmic radiation. Measurements on the tritium content in ice layers of glaciers and polar ice caps indicated an increase in the galactic cosmic ray flux during quiet solar period as also the direct solar emission during active period. Measurements on carbon 14 content indicated that cosmic radiation has remained at a roughly constant level for the last few thousand years. Similar studies with several other isotopes of longer lifetimes indicated that within *c.* a factor of 2, cosmic ray flux has remained constant during the last few million years! From the point of view of establishing the origin, acceleration, distribution and storage of high energy particles in the universe, it is important to know whether this constancy extends to periods greater than 100 million years. Present evidence on K^{40} concentrations, though somewhat unreliable, seems to indicate that no gross intensity variations have occurred for *c.* a billion years!

High Energy Interactions

The afternoon session on 10 December introduced the topic of High Energy Interactions. From data obtained from air shower experiments, conclusions drawn regarding several parameters pertaining to high energy interactions were presented. Parallel sessions on Modulation considered modulation effects on galactic cosmic rays at various parts of the solar cycle. It was pointed out that the changes during the rise and fall of solar activity are not similar, as seen from the data for the last solar cycle.

The morning session on 11 December was again devoted to High Energy Interactions. Dr B. M. Udgaonkar gave a review talk on the Theoretical Aspects of High Energy Interactions. This was followed by a review talk by Dr W. O. Lock on Experimental Work at Accelerators on Particle Creation in Multi-GeV. Region. Several other workers described the results of studies pertaining to this problem. In the afternoon, parallel sessions on High Energy Interactions and Modulation were held. The former session discussed experimental details about the structure of air showers and jets and other related phenomena such as energy and charge spectra of the constituent particles. The session on Modulation dealt with changes in energy spectra of cosmic rays with solar and geomagnetic activity and also discussed the problem of diurnal variations. The tendency for a 27-day recurrence in diurnal variations of night type maxima was demonstrated. Estimates of the temperature effect indicated effects less than 0·1 per cent at least at high latitudes.

The early morning session of 12 December also was devoted to High Energy Interactions. Dr M. Koshiba gave a review talk on recent large stack investigations of high energy jets. This was followed by a talk by Dr Y. Fujimoto on emulsion chamber project conducted with Japanese-Brazilian collaboration. Some interesting facts that have emerged from these investigations are: (1) the one-pion multiperipheral model cannot be regarded as the dominant mode of high energy interactions; (2) the mean free paths do not have different values at higher energies; (3) in the centre of mass system, emission of secondary particles is asymmetric; (4) the forward surviving baryon carries on the average 50 per cent energy and the average inelasticity is *c.* 0·5; and (5) the multiplicity follows roughly a $E^{\frac{1}{4}}$ law in a wide energy band and does not seem to depend on the mass of the incoming particle.

Neutrino Physics

In the morning session on 12 December, the topic of Muons and Neutrinos was introduced. Dr A. M. Wolfendale gave a review talk on high energy muons and Dr P. V. Ramana Murthy spoke about the intensity measurements of cosmic rays deep underground and energy spectrum of muons at sea level. The results of recent measurements of the energy spectrum over the range 1-10000 GeV. were presented. The underground experiments have indicated that the slope of the integral production spectrum is *c.* −1·65 at energies of *c.* 600 GeV. but increases to *c.* −2·50 at energies of *c.* 3000 GeV. The afternoon parallel sessions were devoted partly to Modulation where associated changes between solar phenomena and diurnal variation of cosmic rays were discussed and some evidence for a sidered daily variation of cosmic rays underground was also presented, and partly to High Energy Interactions. The late evening session was again devoted to Muons and Neutrinos where further experimental results of mu-meson measurements were presented and discussed. In parallel, a meeting was held to discuss the programme for the coming International Quiet Sun Year (IQSY).

The early morning session on 13 December discussed the theoretical aspects of High Energy Interactions. Dr E. L. Feinberg gave a review talk on Cosmic Rays and Theory of Strong Interactions. This was followed by a talk by Dr B. Peters on Meson Production at High Energies and the Propagation of Cosmic Rays through the Atmosphere, wherein a very simple model of interactions was presented. This was further elaborated in the paper by Dr Yash Pal. According to this model, the main features of the meson production process are: (1) a fairly isotropic emission of mesons from a fireball moving with small velocity in the C-system of a nucleon-nucleon collision; and (2) the emission of mesons from various excited baryon states, the nature of which is independent of collision energy above 10-15 GeV. Calculations based on this simple model seem to represent existing experimental data adequately. Fluctuation problems in electromagnetic cascades were also discussed. The parallel session on Modulation discussed several papers relating to geomagnetism and rigidity spectra. Some useful calculations of vertical cut-off rigidities based on sixth degree simulation of geomagnetic field were presented.

The afternoon session was devoted to Neutrino Physics. Dr G. Feinberg reviewed the known properties of neutrinos while Dr D. H. Perkins reviewed the present status of neutrino experiments with accelerators. The present position in this field may be summarized as follows: (1) there are at least 2 distinct types of neutrinos, viz. γ_e and γ_μ, the former occurring in the decay of a neutron to proton and electron, and the latter in the decay of a pi-meson to a mu-meson; (2) their other properties are almost alike; (3) electric charge of the neutrino is less than 1/10000th of electronic charge and mass less than 1/200th of electronic mass; spin is $\frac{1}{2}$ but statistic is not known; and (4) both types of neutrinos have very weak interactions in general. In spite of the incomplete information, several interesting experiments have been performed and several others are planned for future.

The sessions on 14 December dealt again with Muons and Neutrinos. Dr H. Y. Chiu gave an interesting review of Neutrinos in Astrophysics. There are some definite astrophysical processes in which a part of stellar energy is converted into neutrinos. For example, the nuclear energy of our Sun comes 90 per cent from proton-proton reaction and 10 per cent from carbon-nitrogen-oxygen cycle. Both these processes give neutrinos. In general, *c.* 20 per cent of the total energy a star emits during its lifetime is in the form of neutrinos! Near our earth, cosmic rays produce secondary neutrinos in their interaction with the earth's atmosphere. Neutrinos can be detected by a few, though very difficult, methods and work in this direction is in progress. Dr M. G. K. Menon gave an account of the TIFR experiments deep underground. Dr M. Crouch described some experiments proposed to be undertaken in Africa. Some new results may be expected to be presented at the next cosmic ray conference.

Concluding Session

The last session on the evening of 14 December was devoted to a general discussion of the various topics. Dr K. McCracken summarized the proceedings of the sessions on Modulation, Dr G. D. Rochester those of the sessions on Muons and Neutrinos, and Dr N. Dobrotin the results on High Energy Interactions. These were followed by general discussions about future plans in these fields.

The conference was very useful for the stimulation of cosmic ray work in India. Foreign delegates appreciated very much the contribution of Indian scientists.

Effect of Drugs on Synthesis & Mobilization of Lipids*

M. SIRSI

Pharmacology Laboratory, Indian Institute of Science, Bangalore

THE recognition of the intimate relationship existing between atherosclerosis and cholesterol has been partly responsible for the intensive research activity in the field of lipid metabolism. It now appears as if the lipid metabolism is more vulnerable than carbohydrate metabolism and is easily influenced by drug, diets, stress and other environmental factors.

Study of the influence of diet, which used to be the domain of nutritionalists, has now been invaded by the biochemists who are interested in knowing the alteration in metabolic patterns as a result of dietetic variations. Since this in turn is closely linked to disturbances of functional activities of organs, pharmacologists are not far behind to enter the field with their interest in the drugs which could correct the deranged metabolism.

Mechanism Affecting Bile Acid Formation

An understanding of the factors involved in the synthesis and metabolism of bile acids is essential to obtain an integrated picture of the cholesterol metabolism of the individual.

Bile acids are important constituents in the excretory pathways of cholesterol. As the cholesterol ring system is metabolically stable, it is not totally degraded in the mammalian cell. The cholesterol molecules that leave the organism do so as cholesterol or as some closely related C_{27} compounds, as bile acids and to a minor extent as C_{19} or C_{21} steroid hormones or their metabolites. In mammals C_{24} bile acids represent the main excretory products of cholesterol.

Human bile contains the bile acids — cholic, chenodeoxycholic and deoxycholic acids — conjugated with taurine or glycine. Sometimes a small amount of lithocholic acid may be found. The bile acids are reabsorbed in the intestines and pass through a number of times in the enterohepatic circulation before being finally excreted with the faeces.

Like other homeostatic mechanisms in the system, the rate of bile acid formation in the liver is controlled by the amount of reabsorbed bile acids returning to the liver via the portal vein. The inhibition of reabsorption of bile acids results in considerable increase in bile production as could be seen in cases of bile fistula.

The bile acids are considerably altered chemically by the intestinal microorganisms. Tracer studies with C^{14}-labelled cholic acid in germ-free rats have revealed that intestinal microorganisms not only metabolize the bile acids but also influence the rate of excretion with the faeces, as also the total amount of the acids produced.

In most higher animals cholic and chenodeoxycholic acids are the main 'primary' bile acids that are formed in the liver cells and from these the 'secondary' bile acids, deoxycholic and lithocholic acids respectively are formed together with many other metabolites by intestinal microorganisms. The introduction of the 7α-hydroxyl group in the cholesterol molecule appears to be an obligatory step in the formation of the bile acids.

Some salient findings observed by the use of C^{14}-labelled cholic acid in human volunteers are:

The enterohepatically circulating bile acid pool is 3-5 g. and five daily circulations represent a daily excretion of 20-30 g. of bile acids with the bile into the duodenum. During the same time 1-2 g. of cholesterol is also excreted with the bile. Most of the bile remaining in the faeces is normally less than 1 g. A considerable part of cholesterol is also absorbed leaving about 0·3-1 g. of sterols.

The nature of the diet affects the bile salt excretion quantitatively. A change-over from the normal diet can modify the bile acid production even if the fat content is the same in the diets used.

Thyroid hormones, known to markedly affect the cholesterol metabolism, also influence the bile production both qualitatively and quantitatively. Bile acid excretion is considerably reduced in hypothyroid rats and is found mostly as cholic acid. In the hyperthyroid rat while quantity is similar to normal, qualitatively it differs in that more chenodeoxycholic acid than cholic acid is excreted in the bile. A few human experiments have also shown that hypothyroid patients have a lower daily production and/or a larger turnover time than normal, while hyperthyroidism is associated with higher daily production and/or shorter turnover time. Bile acid production is thus seen to vary very much with changing dietary and hormonal conditions.

Pathways of Transport of Fatty Acids and the Role of Catecholamines and the Sympathetic Nervous System

The last five years have witnessed rapid advances in our understanding of pathways of fatty acid transport in the blood and of factors regulating fat mobilization and deposition.

Free fatty acids (FFA) and triglycerides (TGL), rather than fatty acids associated with phospholipids and cholesterol, appear to be the major contributors to transport of fatty acids from one part of the body to another.

The circulating FFA are derived primarily from adipose tissue, turn over with great rapidity and constitute the chief source of fatty acids available to peripheral tissues for oxidative metabolism. The extent to which these fatty acids are oxidized depends, in part, on the rate of esterification in the tissues which in turn is controlled by the availability

*This review is based on *Effects of drugs on synthesis and mobilization of lipids*, Vol. 2, Proceedings of the First International Pharmacological Meeting, 1961, edited by E. C. Horning (Pergamon Press Ltd, Oxford), 1963.

of alpha glycerophosphate derived from glucose. A large part of FFA is immediately esterified to form TGL in the liver.

The TGL formed as above or derived from diet and lipogenesis are the main sources for the circulating TGL. In the post-absorptive state, FFA are the major source of circulating TGL. TGL derived from the bile are present in all plasma lipoproteins and the very low density lipoproteins constitute their major form of transport. These low density lipoproteins can be taken up without prior hydrolysis into the liver parenchymal cells, while hydrolysis catalysed by the enzyme, lipoprotein lipase, is involved in the extra hepatic tissue uptake. Increased lipase activity with rapid re-esterification of fatty acids within the cells is the mechanism for directing triglyceride fatty acids into adipose tissue in the fed state.

There is considerable evidence that the sympathetic nervous system, by liberating its neurohormones, plays a role in the fatty acid metabolism in the normal animal. Recently it has been shown that sympathetic nervous activity influences mobilization of FFA from adipose tissue. Stimulation of the sympathetic activity, as by orthostatic stress or fear and discomfort, increases the plasma concentration of FFA while depression by ganglionic blockade lessens the FFA level.

Drugs influencing the sympathetic nervous system activity also affect the mobilization of FFA. Chloropromazine and meprobamate lessen the FFA increase after electrical stimulation. Nicotine, probably by stimulating the sympathetic ganglia, increases the FFA concentration. Besides adrenal medulla, extra adrenal part of the sympathetic nervous system also plays an effective role in this mobilization.

Plasma concentration of FFA increases during fasting, but the mechanism of action is far from clear.

Fatty acid mobilization, fatty liver and hyperlipidaemia occurring in uncontrolled diabetes mellitus may also reflect, in part, the sympathetic nervous activity of the individual.

FFA mobilization induced by catecholamines is dependent on other hormonal factors and is probably species specific.

The increased lipoprotein concentration seen in subjects prone to coronary heart disease may also be explained on the basis of hypertonic activity of the sympathetic nervous system.

Nervous System Regulation of Release of Free Fatty Acids from Adipose Tissue

Biochemical processes supplying the energy needed to carry out metabolic activities are under the control of the nervous system and are an integral part of the behavioural patterns.

Besides the conservation of heat, increased heat production is essential to maintain constancy in the body temperature in very cold environments. This is done by mobilization and oxidation of additional FFA and glucose.

After chloropromazine administration, rats are unable to maintain the body temperature when kept in cold at 4°C. unlike the normal animals. This suggests that chloropromazine interferes with energy procerses ordinarily activated by cold exposure.

Catecholamines play a prominent role in mobilizing the substrates needed to meet the enhanced energy requirements in the cold. This has been proved by the use of the ganglion blocking agent — chlorisondamine — by chemical sympathetectomy with α-methyl-*m*-tyrosine and reserpine and by N-*ortho*-chlorobenzyl-N′,N″-dimethylguanidine in adrenal demedullated rats. In these chemically sympathetectomized animals, the levels of FFA and glucose in the plasma are not increased as observed in normal animals.

These experiments also indicate that the mobilization of FFA from adipose tissue is a function of the sympathetic nervous system and that catecholamines are an absolute requirement in the mobilization of both FFA and glucose and that temperature cannot be maintained if the sympathetic nervous system is blocked.

In the attempt to study the mechanism of action of drugs in causing fatty infiltration of the liver, it has been observed that ethanol and morphine cause a stimulation of the pituitary adrenal system and an increase in the plasma levels of the FFA. The presence of linoleic acid in the fatty liver, which is not synthesized by the rats, clearly reveals that the liver TGL is mobilized from the adipose tissue.

An intact sympathetic nervous system is necessary to cause these lipid changes. Chlorisondamine, a ganglion blocking agent, and dibenamine, an adrenergic blocking agent, counteract the effects of ethanol on plasma FFA and liver TGL. The lipid changes, similar to those caused by morphine and ethanol, induced by ACTH are also counteracted by chemical sympathetectomy by the ganglion blocking drugs, reserpine and BW 392C60. These studies indicate the need of the sympathetic nervous system and the peripheral catecholamines for the action of ACTH on the adipose tissue.

In vitro studies on the release of FFA from the adipose tissue by ACTH have confirmed the need of norepinephrine for this metabolic action, but the concentration of the polypeptide hormone incubated with the fat pads is much higher than that likely to be met within the body.

Besides the catecholamines, adrenal corticoids also appear to be essential for the energy mobilization from adipose tissue.

The explanation for this dual requirement of both sympathetic and adrenocortical systems for mobilizing energy sources is far from clear. The electrolytic changes induced by the corticoids may probably influence the permeability of the cell membranes to the catecholamine and thus exert the observed actions conjointly.

Synthesis, Accumulation and Release of Triglycerides by Liver

Many biochemical processes involved in lipid metabolism in the rat can be altered by the administration of drugs. Some of the changes in the synthesis, accumulation and release of TGL may be due to the direct action of the drug on specific enzyme systems and others may be a resultant of hormonal actions.

Liver TGL, plasma FFA and plasma corticosterone levels are elevated by stimulation of the pituitary adrenal axis. ACTH is the hormone responsible for initiating these changes. The presence of norepinephrine in adipose tissue is essential for the mobilization of lipids by ACTH.

Though a triglyceride fatty liver can be produced by the administration of a single large dose of the pharmacologically active compounds as ethanol, carbon tetrachloride or ethionine, each agent exhibits different lipid metabolic pattern.

Five to twenty-five fold increase in liver TGL and triglyceride linoleic acid is observed after stimulation of pituitary-adrenal axis by ethanol, carbon tetrachloride and ethionine. Since linoleic acid is not synthesized by the rat, this large increase in triglyceride linoleic acid may be ascribed to transport from the depots to the liver, rather than from *de novo* synthesis in the liver. Impaired hepatic release of TGL after carbon tetrachloride or ethionine and increased mobilization of fatty acids after ethanol are factors contributing to this high glyceride level.

The possible enzymatic changes in lipid synthesis after drug treatment has been studied by the incorporation of albumin bound 1-C^{14} palmitate in liver lipids by homogenates from livers of normal and treated rats. The liver homogenates of treated rats always incorporate more of the total radioactivity into TGL and less into phospholipids. Cytidine-5′-diphosphate choline had no effect on fatty acid incorporation after carbon tetrachloride treatment; in ethionine-treated rats it decreased the incorporation of fatty acids into TGL but had no discernible influence on phospholipids. The effect of ethanol, on the other hand, was reversed by this compound. After carbon tetrachloride and ethionine treatment, the activity of phosphoryl choline glyceride transferase is found to be affected.

In vivo, the liver TGL content was the same in the control, hypophysectomized and ethanol-treated hypophysectomized rats. The decreased synthesis of TGL from 1-C^{14} palmitate and increased incorporation of the fatty acid into phospholipids, observed in hypophysectomized rats, were not in any way affected by ethanol treatment.

In vivo, carbon tetrachloride stimulated the deposition of liver TGL in hypophysectomized rats to a slight extent. However, no effect on enzymic pattern of incorporation of palmitate was seen *in vitro*. The accumulation of TGL in hypophysectomized rats after carbon tetrachloride treatment appears to result from impaired release from liver to plasma. Ethionine like carbon tetrachloride also impairs the release of TGL from the liver.

Sex difference in the enzymic incorporation of fatty acids into liver lipids, after treatment with ethanol and ethionine, has been observed. Fatty acids are incorporated into phospholipids more readily than into TGL in homogenates from male rats.

Cholesterol Turnover in Man

While studying the overall balance of cholesterol metabolism one has to bear in mind that most cells can synthesize cholesterol from acetate via mevalonate, squalene and lanosterol. The problem of regulation of serum cholesterol concentrations in man requires some estimate of the rate of endogenous synthesis.

The methods used to study the turnover are: measurement of the time required for total body cholesterol to reach a constant content of deuterium after administration of D_2O; rate of decrease in specific activity of serum cholesterol after giving acetate-2-C^{14}; administration of cholic acid-24-C^{14} and measuring the rate of its specific activity in bile. A recent technique utilizes the high rate of incorporation of mevalonic acid-2-C^{14} as a means to study cholesterol turnover in man. This also permits a long-term study of cholesterol turnover. The results of these studies indicate that there are two dominant metabolic pools; one with a relatively slow turnover and a smaller one representing the cholesterol in rapid exchange with plasma and liver, i.e. the plasma-liver pool. The latter appears to be unaffected by the size of the body pool. Depending on the magnitude of the pool, the rate of cholesterol synthesis is of the order of 1-4 g./day.

Action of Cholesterol Synthesis Inhibitors

Application of gas chromatography to the analysis of mixtures of higher molecular weight compounds has provided a quick, convenient and dependable method for studying the intermediary products in the metabolic pathway involved in the conversion of squalene to cholesterol. This technique has facilitated the study of the effects of hypocholesterolaemic compounds on cholesterol metabolism. It is essential to know the nature of the intermediary compounds accumulating as a result of the inhibition of cholesterol synthesis and understand their effects on the host prior to testing the clinical efficacy of such compounds.

Presence of desmosterol in small amounts in many of the tissues of the normal rat has been reported. Gas chromatography has shown that desmosterol represents 70-75 per cent of the total skin sterols. Triparanol and its trifluoro methyl analogue, amongst the many hypocholesterolaemic agents studied, cause a definite accumulation of desmosterol in a number of different tissues of the drug-treated rats. Though the same results were obtained earlier by colorimetric methods, the application of gas chromatography to the analysis of mixtures of sterols, steroids and bile acids has certainly provided an easy reliable technique, the lack of which had so far been a deterrent for rapid progress in this field.

Since desmosterol accumulates in the serum and tissues of patients during triparanol administration, it would be interesting to know how far this compound can be a precursor of the physiologically important compounds in place of the normally utilized cholesterol.

The conversion of desmosterol to two classes of cholesterol metabolites, viz. bile acids and steroid hormones, has been studied by using 2-C^{14} mevalonic acid in subjects receiving triparanol and following the labelling in plasma desmosterol, bile acids of the bile collected by duodenal incubation and in the steroid derivatives extracted from the

urine. The C^{14} specific activities of the purified bile acids and steroids were then compared with the specific activities of purified plasma desmosterol and cholesterol. In a more elaborate study, simultaneous injections of mevalonate and tritium-labelled cholesterol were given and the specific activities of the components were determined as before. The results show that 25 ± 10 per cent desmosterol is converted to cholesterol and approximately three-fourths goes in for the conversion to bile acids and other sterols.

In *in vivo* studies, comparing desmosterol and cholesterol as substrates for enzyme systems from the liver mitochondria of triparanol-treated mice, both sterols were found to be satisfactory substrates. These experiments confirm that desmosterol and cholesterol are very similar in their effectiveness as substrates for several metabolic pathways.

Alterations in Serum Lipid Patterns: Oral Administration of Synthetically Prepared Arachidonic Acid

The depressant effects of certain dietary fats on serum lipids of man is now well recognized and it has also been proved that the hypolipidaemic effect is due only to their content of unsaturated fats.

The effect of synthetically prepared fatty acids on cholesterol levels is now under investigation in many laboratories. Synthetic arachidonic acid containing 85-95 per cent *cis*-5,8,11,14-eicosatetraenoate and traces of behenic acid and few unidentified components has shown a tendency for decreasing serum levels of total lipids as well as phospholipids and cholesterol to varying degrees in normal and in a few cases of essential hyperlipaemic persons. The efficiency of synthetic arachidonate in lowering the serum lipid fractions was thought to be equal to that of the arachidonate prepared from natural sources.

Effect of Triton WR 1339

Administration of Triton WR 1339 induces hyperlipaemia and hypercholesteraemia. A detailed analysis of the lipid and cholesterol levels in rats after feeding olive oil and administering Triton intravenously has revealed that Triton does not have any influence on the intestinal absorption of fat and the hyperlipaemic condition is due to the blocking of the disappearance of cholesterol and triglycerides from the blood.

Mode of Action of Hypolipaemic Drugs

Administration of heparin, dibazole or benzohexonium simultaneously with cholesterol feeding in rabbits has been shown to result in marked inhibition in the onset and development of atherosclerosis. Benzohexonium decreases the cholesterol lecithin ratio by augmenting of blood cholesterol to a less extent than of lecithin.

Dibazole also reduces the cholesterol : lecithin ratio, but the reduction is due to a considerable rise in blood lecithin level. There have been suggestions that lecithin might contribute to maintaining cholesterol in a colloid state, thus preventing its deposition in blood vessel walls.

Ethyl phenylacetic acid and vanadium also inhibit the onset and development of experimental atherosclerosis. The actions of these are not restricted to inhibition of cholesterol synthesis but also their breakdown. These two drugs act synergistically when administered together.

Primary importance in the pathogenesis of experimental cholesterol atherosclerosis should not be attributed to the absolute value of blood cholesterol but rather to its relationship to blood lecithin, as it contributes to the maintaining of cholesterol in a colloid state, thereby preventing its deposition in the vessel wall.

Salicylates and chloropropamide, known to be hypoglycaemic agents, also decrease the plasma FFA level.

Data obtained from isotope experiments and from *in vitro* studies on adipose tissue indicate that the effect of salicylate is related to a decreased flux of FFA from adipose tissue to plasma, probably caused by its influence on the lipolysis of the stored TGL in adipose tissue.

Chloropropamide which also exhibited a decrease of FFA in acute experiments appeared not to influence the release of FFA from the adipose tissue. During long-term treatment, chloropropamide causes a significant reduction of the elevated plasma glycerides in diabetes. The mode of action remains to be elucidated.

Hormonal Control of Lipid Transport in the Isolated Perfused Rat Liver

Lipid content of the liver is altered by endocrine and nutritional balance of the animal. Hepatic metabolism of neutral lipids has been shown to be under hormonal control.

Adrenal steroids appear to depress the maximum rates of lipid uptake whereas somatotropin accelerates uptake by the liver.

Liver perfusion studies with a tripalmitin-1-C^{14}-labelled neutral fat emulsion suggest that the liver is a major source of plasma TGL. A rapid uptake of TGL by livers from fasting animals than fed rats is seen; in contrast non-esterified fatty acids are taken up from the perfusate at identical rates by livers from both fed and fasted rats. A net increase in perfusate TGL is observed from the liver of fed animals but not from fasted rats.

These results together with observations after perfusion of starved and fed livers, with the blood of each to the other, suggest a hormonal control of the uptake and release of TGL, more effective on the uptake than on the release.

Influence of Androsterone on Blood Lipids

Estrogens can lower the abnormal lipid values in subjects with atherosclerosis or in cholesterol-fed animals.

Divergent results have been obtained by different investigators in the study of the influence of androsterone on blood lipids and some authors conclude that androsterone, in the doses administered by them, has no depressant action on the blood lipids nor does it reverse the aortic and coronary atherosclerosis induced by high cholesterol regime.

The disparity in susceptibility to atherosclerotic heart disease between men and women is well established.

A study of the oxidation of cholesterol-26-C^{14} by liver mitochondrial preparations in (i) intact and gonadectomized rats of both sexes and (ii) similar rats treated with androgens and estrogens has shown that in the intact rat, mitochondria from female livers oxidize cholesterol to a greater extent than those from male livers; castration enhances cholesterol oxidation in male rats while oophorectomy exhibits no influence.

The results suggest that the sex difference is due to the presence or absence of androgen.

While the shifts in the blood lipids can explain the inhibition of the cholesterol-induced coronary atherosclerosis in chicken by the estrogens, no such direct effect is seen with testosterone. Since dissociation of the anabolic from the androgenic effects has been possible by testosterone derivatives, these analogues have now been used to study the mechanism involved in their hypolipidaemic action.

Metabolic and isotopic studies have shown that testosterone and androsterone stimulate the liver to increase oxidative catabolism and excretion of cholesterol degradation products by the biliary route into the faeces, over and above the stimulatory effect, observed with the atherogenic diet alone. It was also seen that testosterone and androsterone produced significant inhibition of experimentally induced atherosclerosis and increased the rate of absorption of orally administered C^{14} cholesterol from gastrointestinal tract, while the anabolic steroid, 17-ethyl-19-nortestosterone, did not share these effects.

Thyroxine Analogues

It is well known that serum cholesterol levels are raised in hypothyroid subjects and that thyroid hormones can lower the serum cholesterol. Stimulation of cholesterol degradation and excretion is suggested as the mode of action of thyroid hormones in inducing hypocholesteraemia. Since partial dissociation of the various hormonal effects is now possible by thyroxine analogues, the influence of these compounds on certain hormonal effects has been compared.

Of a variety of ethers of 3,5-diodotyrosine, the most potent were 3,5-diodo-2′,3′-dimethyl-1-thyronine and 3,5-diodo-4-(4′-hydroxy-1′-naphthoxy)-DL-phenyl alanine (3,5-diodo-DL-naphthyronine) in their effects on thiouracil induced goitre, oxygen consumption and plasma cholesterol. No compound exhibited only one single physiological effect, though at certain doses one action predominated over others.

3,5,3′-Triiodo-D-thyronine (D-T_3) has a more pronounced initial effect on serum cholesterol than on oxygen consumption in euthyroid subjects, but this isomer increased sharply the oxygen consumption of hypothyroid human subjects.

Study of lipid metabolism in a hypothyroid rat after administration of D-T_3 showed restoration of the total body oxygen consumption from a hypothyroid level to within 10 per cent of euthyroid state, increase of QO_2 of myocardial homogenates, reduction in the liver fatty acid content and increase of liver cholesterol concentration. These results indicate that D-T_3 accelerated metabolic turnover of liver fatty acids and increased synthesis of cholesterol in the hypothyroid liver.

Heparin and Lipaemia Clearing Factor

The strong electric negative charge, low osmotic pressure and high molecular weight makes heparin an unusual biological substance from the standpoint of its physico-chemical properties. Heparin has a strong inhibitory action upon the uptake of labelled serum bound lipids by human and animal endothelial type cells, harvested from short-term organ cultures of large arteries.

Lipaemia clearing factor (lipoprotein lipase) is found in mammalian circulation after injection of heparin and synthetic heparinoids. The lipaemia clearing activity induced in mammals by heparin is different from that induced by sulphopolyglycin, a synthetic heparinoid. It is suggested, although not proven, that more than one enzyme system can be formed in the body and that the sulphated polymer is not always a part of the enzyme.

Some Aspects of the Chemotherapy of Cancer

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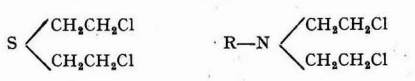
ALTHOUGH cancer is known to mankind for nearly 3500 years, yet up till now no suitable chemotherapeutic agent for its prevention or cure has been found out. There are evidences that various types of cancers have similar characteristics, but some differences do exist among them. Each type of cancer requires different treatment and, hence, one particular drug is not suitable for all types of malignant neoplastic diseases. However, an ideal chemotherapeutic agent for cancer should essentially destroy the malignant cell leaving the normal cell unharmed. But the present drugs are not only toxic to cancer cells but also destroy the normal cells to some extent.

Several types of chemotherapeutic agents, which have been discovered during the last few years for the effective treatment of malignant growth, can be classified broadly into five groups, viz. (i) cytotoxic or alkylating agents, (ii) antimetabolites, (iii) antibiotics, (iv) hormones, and (v) certain miscellaneous agents. Several thousands of chemotherapeutic agents of the above categories have been screened in the hope of getting ideal agent(s) for cancer, but not a single compound has yet been found which can only selectively destroy the cancer cells without affecting the normal tissues.

Cytotoxic or Alkylating Agents

In general, the cytotoxic agents as general cell poisons not only destroy malignant cells but also affect the normal cells and hence their use as chemotherapeutic agents are not specific. The cytotoxic agents are also called alkylating agents on the basis of their chemical properties of alkylating the substance with which they react by a covalent or similar such strong polar bonds. At present sulphur mustards, nitrogen mustards and the corresponding ethylenimines, methane sulphonic esters and certain epoxides are included in this group. The earliest alkylating agent used by Adair and Halsey[1] in 1931 for the treatment of localized lesions of skin cancer was sulphur mustard, or bis-(2-chloroethyl)-sulphide (I), which was synthesized in 1854 by Dr Richie and used by the Germans as a war gas during World War I. But the high toxicity of the sulphur mustards, their low solubility in water, and their vesicant properties prevented them from clinical application for the treatment of the neoplastic diseases.

Shortly after the discovery of the usefulness of the S-mustards in the treatment of neoplasms, attention has been diverted towards the possible use of nitrogen mustards, which are less toxic, can easily form stable salts with hydrochloric and other acids, and the salts are highly soluble in water.

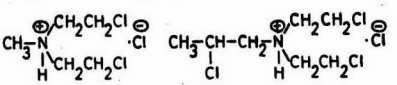


I II

where R=CH_3, C_2H_5, CH_2CH_2Cl, etc.=aryl radicals

The clinical studies of the aliphatic nitrogen mustards in the treatment of Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders were reported by Goodman *et al.*[2] and also by Jacobson *et al.*[3].

The most widely used aliphatic N-mustard in the treatment of cancer is N-methyl-N,N-bis-(2-chloroethyl)-amine hydrochloride (III). It is used in the treatment of Hodgkin's disease, certain type of leukemias and carcinoma of the breast and lung. Penicillin is often administered simultaneously with N-mustards to cut down the chances of other side effects caused by N-mustards. Another aliphatic N-mustard, 2-chloropropyl-bis-(2-chloroethyl)-amine hydrochloride (IV), marketed as Novembichin, is found to be less toxic than the parent N-mustard (II) and possesses the same activity against leukemia and Hodgkin's disease[4].



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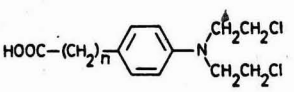
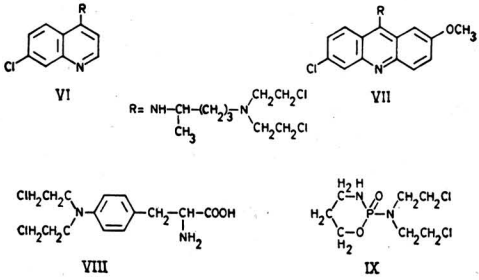


V

Bergel[5] and Haddow and coworkers[6], at the Chester Beatty Research Institute in London, have made an extensive study on the effectiveness of the aromatic N-mustards on malignant diseases. In the phenylbutyric acid mustard series, represented by structure (V), the highest activity in the treatment of a number of human tumours was found when $n = 3$. This compound is marketed in the name of Chlorambucil (Lukeran). Several antimalarial nitrogen mustards were synthesized by Price *et al.*[7,8] from a number of quinoline and acridine antimalarials in which diethylamino group of the side chain was replaced by the bis-(2-chloroethyl)-amino group. The idea was that the quinoline or acridine nucleus might transport the N-mustard moiety at the site of the malignant tumours and thereby selectively destroy the tumour cells leaving the normal cells unaffected. The two compounds, chloroquin and quinacrine mustards (VI and VII), are found to be active against certain types of cancer cells.

In order to take advantage of amino acids as biological carriers by which specific toxic residues might be introduced into cellular metabolism, a number of cytotoxic derivatives of amino acids in the form of alkylating agents have been used[9-13]. It is of interest that one of the most active of these



VI VII VIII IX

as an antitumour agent is *p*-bis-(2-chloroethyl)-aminophenyl alanine[4,5,14-16] (VIII).

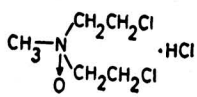
Other derivatives of the alkylating agents of possible interest in cancer, the phosphoroamide nitrogen mustards, depend on the action of an enzyme for activation. Administered in this way, a much higher dose of a nitrogen mustard might be delivered to the cells of a tumour with phosphamidase activity[17] than would reach the cell if the parent N-mustard was administered as such[18-21]. A phosphoroamide N-mustard (IX), the transport form of bis-(2-chloroethyl)-amine which would presumably be converted into the active form at the site of action, has been found inhibitory by Arnold *et al.*[22] against a number of tumours in rats.

Peptide N-mustards would be another class of derivatives of the alkylating agents of the same type which, in addition, are derived from biological carriers. These N-mustards would appear to be a class of compounds worth investigation for possible antitumour properties[13].

The sugar derivative of N-mustard, 1,6-bis-(2-chloroethylamino)-1,6-desoxy-D-mannitol dihydrochloride, has been investigated by Kellner *et al.*[23] for possible antitumour activity.

Yoshida *et al.*[24,25] have shown that N-oxide forms of N-mustards are less toxic than the parent N-mustards and also possess much higher therapeutic ratio than those of the original N-mustards which are evident from Table 1.

The only N-oxide N-mustard that has been experimentally studied and used for the treatment of acute and chronic leukemia and breast cancer is methyl-bis-(2-chloroethyl)-amine hydrochloride N-oxide (X), marketed in the name of Nitromin (Mustron).

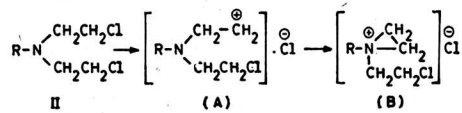


X

TABLE 1 — TOXICITY AND THERAPEUTIC RATIO OF N-OXIDE FORMS OF N-MUSTARDS

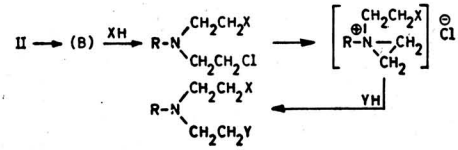
Compound	LD_{50}, rat, intraperitoneally mg./kg.	ED_{50}, Yoshida sarcoma mg./kg.	Therapeutic ratio
$CH_3—N(CH_2CH_2Cl)_2$	1·7	0·1	17
$CH_3—N(CH_2CH_2Cl)_2 \rightarrow O$	80	1·0	80
$CH_2=CHCH_2N(CH_2CH_2Cl)_2$	0·8	0·5	1·6
$CH_2=CHCH_2N(CH_2CH_2Cl)_2 \rightarrow O$	20	1·0	20

Mechanism of reaction — It is generally known that antitumour activity of the N-mustards is due to the formation of highly reactive ethylenimonium ions (B) in polar solvents and at physiological *p*H. The carbonium ion (A) is formed by the elimination of the chloride ion in an aqueous solution[26], but in acidic solutions N-mustards are relatively stable. In the case of N-mustards the reactions involve unimolecular nucleophilic displacements (S_N1) on a carbon atom and this type of reaction is practically independent of the concentration of reacting centres, whereas in the case of imines, epoxides and dimesylates the reactions involve bimolecular nucleophilic displacements (S_N2). The intermediate carbonium ions react with compounds containing easily replaceable hydrogen atoms such as free amino groups of proteins or of adenyl groups, the phosphate groups of nucleic acids, etc.[27]. The weakly basic aromatic mustards probably react with nucleophilic biological agents through a carbonium ion intermediate (A), since their cyclic ethylenimonium intermediates (B) are relatively unstable.

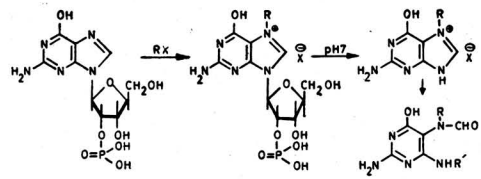


II (A) (B)

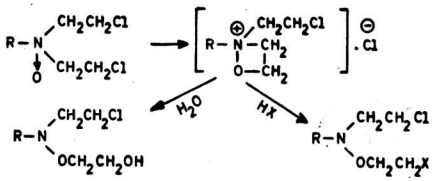
The overall reaction mechanism of aliphatic N-mustards in biological systems can be represented as shown below:



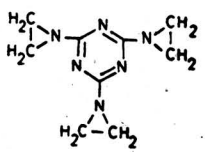
It has been observed by Davis and Ross[28] that chloroethylamines form more stable linkages with phosphoryl groups than carboxyl groups in proteins. Elmore *et al.*[29] have also suggested the possibility of cross-linking mechanism in an attempt to explain the cytological action of mustard gas on the nucleic acids. From the work of Press and Butler[30] it is evident that the reaction of N-mustard with purine nucleosides and thymus nucleic acid involves the alkylation of guanosine or adenosine moiety of the parent substances. Lawley[31] has shown that alkylation of guanylic acid by N-mustard takes place at 7-position and the resulting intermediate compound, after removal of the sugar residue, breaks down according to the following scheme:



The reaction mechanism of N-oxide nitrogen mustards with biological system can be represented as shown below:



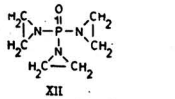
Other cytotoxic agents—From the observation that N-mustards cyclize in polar solvents to the intermediate ethylenimonium ions of the type (B), it was thought that the application of ethylenimine type of compounds might be more effective antitumour agents with lesser toxic side effects than those of N-mustards. With this idea in view Crossley and his associates[32-34] first reported that 2,4,6-tris-(1-aziridinyl)-*s*-triazine (triethylenemelamine, TEM, XI)



XI

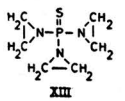
could inhibit the experimental tumours in mice. Several such compounds have been prepared and experimentally proved to be effective antitumour agents, of which compounds (XII-XV) are the most widely used.

TEM (XI) is twice as active and twice as toxic as N-mustard in the treatment of some of the neoplastic diseases and can be administered orally. TESPA (XIII)[35] is better than TEPA (XII)[36,37] in the treatment of Hodgkin's disease, cancer of the stomach and carcinoma of the breast. The quinones (XIV and XV)[38-40] are found to be effective against Hodgkin's disease, cancer of the stomach and chronic lymphatic leukemias, and can be administered either orally, intravenously or intratumorally.



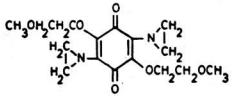
XII

Tris (1-aziridinyl) phosphine oxide (TEPA)



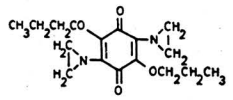
XIII

Tris (1-aziridinyl) phosphine sulphide (TESPA)



XIV

2,5 - Bis (1-aziridinyl)- 3,6 - bis (2-methoxy ethoxy)-1,4 - benzoquinone



XV

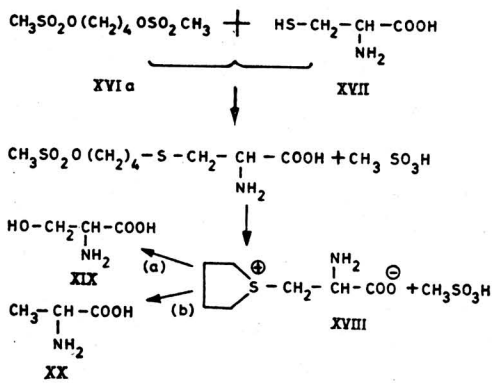
2,5-Bis (1-aziridinyl)- 3,6 - di-*n*-propoxy -1,4- benzoquinone

A new type of bifunctional alkylating agents possessing antineoplastic activity has been investigated in a series of compounds belonging to sulphonic acid esters and in particular the α,ω-methanesulphonyloxyalkanes (XVI)[41,42]. The activity of

$$CH_3SO_2O(CH_2)_nOSO_2CH_3$$

XVI

this type of compounds was shown where n is 2-10, but the maximum activity was shown where n is 4 or 5, less where n is 6, 7 or 8 and very greatly reduced where n is 2, 3, 9 or 10. The mechanism of reaction of such type of compounds with amino acids has been shown by Roberts and Warwick[43]. They have demonstrated with the help of radiochromatography that the powerful intermediate thiophenium ion (XVIII), which is formed by the interaction between 1,4-dimethanesulphonyloxybutane (XVIa) and cysteine (XVII), ultimately yields either serine (XIX) or alanine (XX) depending upon the direction of hydrolytic attack causing the $\overset{\oplus}{S}$–C bond fission, as shown below:



XVIa XVII XIX XX XVIII

However, it is still to be a matter of investigation whether this type of reaction takes place with polypeptide or protein molecules.

Antimetabolites in Cancer Chemotherapy

The concept of antimetabolites in chemotherapy was the result of the work of Woods and Fildes[44-46] who showed that *p*-aminobenzoic acid (PABA) was an essential metabolite of bacterial cells and the structurally related compound sulphonamide competed for the bacterial enzymes responsible for the metabolism of PABA. It was later published that sulphonamide and PABA compete for the same enzyme receptors and that bacteriostatic action of sulphonamide is reversed by an excess of PABA.

According to the theory propounded by Woods and Fildes, new chemotherapeutic agents might be obtained by simple modifications of the structure of essential metabolite so that they will react with the same enzyme system but lack the activity of the parent metabolite. This theory has opened up a new chapter in the field of chemotherapy and is

responsible for the synthesis and application of a host of structural analogues of vitamins, hormones and amino acids.

In the case of competitive inhibition of proteolytic reactions, it has been assumed that both the metabolite (substrate) and the inhibitor compete for the same reactive groups of the enzyme, whereas in the case of non-competitive inhibition of proteolytic reactions, the inhibitor, instead of combining directly with the enzyme system, may combine with the enzyme-substrate complex forming an inactive enzyme-substrate-inhibitor complex. Mathematical expressions in respect of the above two types of reactions are well known[47–49].

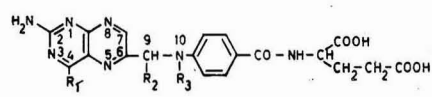
The first application of the antimetabolite principle in cancer chemotherapy was studied by Farber and his associates[50], who used folic acid antagonists for the treatment of leukemia. Further research on the biochemistry of folic acid and search for other antitumour agents, based on the antimetabolite principle, led to the discovery of purine and pyrimidine derivatives which were found to be both folic acid and purine antagonists[51]. Other classes of promising antimetabolites belong to the group of amino acid, vitamin and hormone antagonists.

In order to understand clearly the important role of antimetabolites in cancer chemotherapy, some knowledge about the biochemistry of nucleic acids, their functions and biosynthesis in the biological system is desirable. Nucleic acids[52] are polynucleotides, consisting of four nucleotides, viz. (i) adenylic acid, (ii) guanylic acid, (iii) cytidylic acid, and (iv) uridylic acid, linked together in a specific pattern. A nucleotide unit is composed of three components — a nitrogenous base, a sugar and phosphoric acid. The desoxyribonucleic acid (DNA), which is confined to the nucleus, contains thymine as one of the bases and the sugar component is desoxyribose. The ribonucleic acid (RNA), which is mostly present in the cytoplasm and also found in the nucleus, has uracil as the base and the sugar moiety is ribose. Recent studies have revealed the great importance of DNA as the carrier of genetic information and the important role of RNA in protein synthesis. These two constituents play a very important role in the growth process of cells and protein biosynthesis. It is quite obvious that some of the specific biological effects produced by the various antimetabolites may interfere, at least in part, with the normal biological functions of the nucleic acids and this is the basis of modern aspect of cancer chemotherapy with antimetabolites.

Biochemically, folic acid (XXI), a vitamin responsible for normal growth, is concerned with 1-carbon unit metabolism[53–55] in the conversion of glycine to serine, homocysteine to methionine, ethanolamine to choline, niacinamide to N′-methyl niacinamide, pyrimidine intermediate to thymine, in the introduction of C-2 and C-8 in purine biosynthesis. It has been shown that in 1-carbon unit metabolism folic acid (XXI) acts through reduction and reversible formylation[56–64]. Hence, folic acid (XXI), through its formyl derivative, participates in the *de novo* pathway for the synthesis of polynucleotides from which nucleic acids and then nucleoproteins are derived.

Antifolics — The important work concerning the modification of the parent structure of folic acid (XXI) to get antimetabolites of promising result was directed in three ways, viz. (i) the replacement of the hydroxyl group at 4-position in the pteridine nucleus by an amino group, (ii) substitution on the 9- or 10-positions, and (iii) modification of the glutamic acid chain or its replacement by some other amino acids. An excellent review on a number of folic acid analogues and their biological activity has been published by de Clercq[65] in 1956.

Two most outstanding folic acid antagonists, which are tested and used for the treatment of some of the neoplastic diseases, are 4-aminopteroylglutamic acid (aminopterin, XXII) and 4-amino-N^{10}-methylpteroylglutamic acid (amethopterin, XXIII). Some of the important antifolics of clinical use are compounds (XXI-XXV)

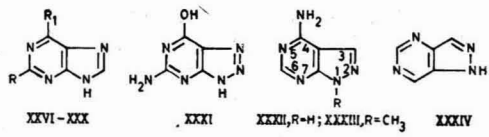


XXI folic acid, $R_1=OH$; $R_2=R_3=H$
XXII aminopterin, $R_1=NH_2$; $R_2=R_3=H$
XXIII amethopterin, $R_1=NH_2$; $R_2=H$; $R_3=CH_3$
XXIV aminopterin, $R_1=NH_2$; $R_2=CH_3$; $R_3=H$
XXV adenopterin, $R_1=NH_2$; $R_2=R_3=CH_3$

The highest antileukemic activity is found in the compounds with 4-amino derivatives. These folic acid analogues are found to interfere with the conversion of folic acid to citrovorum factor or folinic acid[66,67]. All these substances are found to show toxic effects at therapeutic doses and they depress haematopoiesis. Continued use of these products develops drug resistance. However, antifolic acid derivatives are most effective in the treatment of acute leukemia in children and are being used extensively for such purposes.

Among the other synthetic antifolics tried as chemotherapeutic agents are 6,7-disubstituted 2,4-diaminopteridines[68–72], naphthopteridines[73,74], indolopteridines[69], diaminochlorophenylpyrimidines[75], phenyl dihydrotriazines[76–80], arylazopyrimidines[81,82] and amino-8-aryl-8-azapurines[81,82]. None of the compounds of the above groups is as effective as either aminopterin or amethopterin.

Purine and pyrimidine antagonists — A large number of compounds related to purine and pyrimidine have been synthesized and tested for anticancer activity on the presumption that these compounds might act as antagonists to purine metabolism and thus act by interfering with nucleic acid biosynthesis. Out of a series of purine antagonists (XXVI-XXXIII), 6-mercaptopurine (XXVII) has been studied most extensively in experimental animals[83,84]. It is useful for the treatment of acute leukemia in which children generally respond more favourably to the drug than do adults. The chief toxic effects are the hypoplasia of the bone marrow and ulceration of the gastro-intestinal epithelium. This drug is



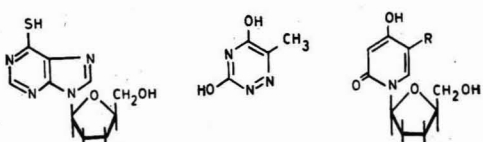
XXVI–XXX XXXI XXXII, R=H; XXXIII, R=CH_3 XXXIV

XXVI $R=R_1=NH_2$
XXVII $R=H$; $R_1=SH$
XXVIII $R=H$; $R_1=Cl$
XXIX $R=NH_2$; $R_1=SH$
XXX $R=H$; $R_1=SCH_3$

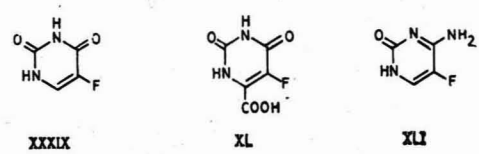
ineffective in chronic lymphocytic leukemia, multiple myeloma, Hodgkin's disease and other metastatic carcinoma and sarcoma. The 6-chloropurine (XXVIII) inhibits the growth of S-180 and produces remission in some acute leukemia and chronic myelocytic leukemia[85,86]. Thioguanine[86] (2-amino-6-purinethiol, XXIX) proves no superiority over 6-mercaptopurine. The activity of 6-mercaptopurine does not improve either on S-alkylation or S-arylation. Clinical trial of 6-mercaptopurine riboside[87] (XXXV) did not show any better result than that of the parent compound, 6-mercaptopurine.

Another series of purine antagonists with some antitumour activity in experimental animals have been obtained by slight modifications of purine ring systems. The first such modified compound 8-azaguanine (XXXI) was synthesized by Roblin *et al.*[88] and later tested as an antitumour agent with no positive result. Another series of compounds, prepared by Robins and his associates[89–92], belonging to a class known as pyrazolo-(3,4-*d*)-pyrimidines (XXXII), were shown to possess tumour inhibitory activity in animals[93]. Out of a large number of compounds tested in this series, only two show activity in preliminary tests. These compounds are 4-aminopyrazolo-(3,4-*d*)-pyrimidine (XXXII) and 4-amino-1-methylpyrazolo-(3,4-*d*)-pyrimidine (XXXIII). However, all the derivatives of pyrazolo-(4,3-*d*)-pyrimidine series (XXXIV) are inactive[94]. An excellent review describing a number of other ring systems analogous to purines has been presented by Timmis[95] in 1957. A thymine antagonist, 6-azathymine (XXXVI), does not cause remission of leukemia in animals or in clinical cases that are resistant to antifolics and 6-mercaptopurine. The uridine derivatives[96], 5-aminouridine and 5-hydroxyuridine glucose derivatives (XXXVII and XXXVIII), have been found to increase the survival time of experimental animals with leukemia 82.

Some of the fluoro derivatives of uracil and orotic acid have shown antitumour activity amongst which mention may be made of two compounds in the above series, which are 5-fluorouracil (XXXIX) and 5-fluoroorotic acid (XL). The former compound (XXXIX) shows considerable activity against ten different transplanted tumours[97]. However, a closely related compound, 5-fluorocytosine (XLI), is inactive against experimental tumours. In spite of the toxicity shown by 5-fluorouracil (XXXIX) at the therapeutic dose, this drug is gradually gaining a place in cancer chemotherapy.



XXXV XXXVI XXXVII, R = NH_2 XXXVIII, R = OH

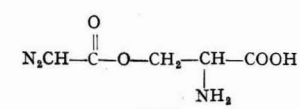


XXXIX XL XLI

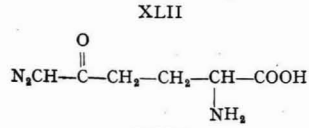
Other pyrimidine analogues[98], synthesized and found active in various degrees against experimental tumours, include 6-azauracil, 6-azauridine, 6-azathymidine, 6-uracil sulphonamide, 6-uracil methyl sulphone and 6-uracil benzyl sulphone.

The mode of action of the various purine and pyrimidine analogues in the biological systems has not yet been clearly understood. However, from the work of Skipper *et al.*[83,84] it can be supposed that these antimetabolites interfere with the biosynthesis of nucleic acids. The mechanism of action of fluorouracil and fluoroorotic acids is perhaps by blocking the conversion of formate to the methyl group of thymine.

Amino acid and antibiotic antagonists — A number of amino acid analogues has been synthesized with an idea that these analogues might be competitive antagonists for the essential amino acids in tumour cells. More particularly the serine and methionine analogues might prevent the biosynthesis of nucleic acids which are more important to the cancer cells than to the normal cells. Ethionine, the ethyl analogue of methionine, has too many toxic effects and possesses very little antitumour activity[99]. Weisberger and Suhrland[100] have reported a class of antagonists which are the selenium derivatives of the amino acids in which sulphur is being replaced by selenium, for the cystine-cysteine system of leukocytes. The requirement of L-cysteine for growth by leukemic leukocytes is more than that of normal leukocytes and hence selenium analogues take the advantage of this requirement. The best known amino acid antagonists are azaserine[101,102] (XLII) and 6-diazo-5-oxo-L-norleucine[103,104] (XLIII, DON). These two antitumour agents act as glutamine antagonists in the synthesis of formylglycinamide ribotide[105–107]. DON is more active than azaserine against Crocker mouse sarcoma 180 and other transplanted cancers.



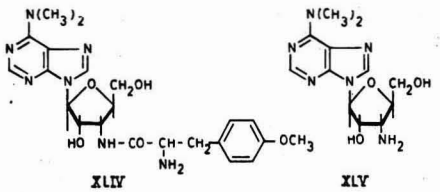
XLII



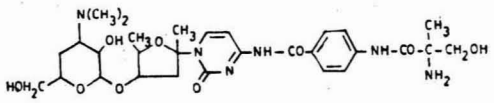
XLIII

Puromycin (Stylomycin, XLIV), isolated by Porter *et al.*[108] from the culture filtrates of *Streptomyces alboniger*, is chemically 6-dimethylamino-9-(3′-*p*-methoxy-L-phenylalanylamino-3′-deoxy-D-ribosyl)-purine[109], which on hydrolysis produces 6-dimethylaminopurine, *p*-methoxy-L-phenylalanine and 3-amino-D-ribose. 6-Dimethylamino-9-(3′-deoxy-β-D-ribofuranosyl)-purine[110-112] (XLV) shows more activity than the parent antibiotic (XLIV) against mammary adenocarcinoma in the C_3H mouse[113].

Amicetin (XLVI), a cytosine containing antibiotic, isolated from several Actinomycete strains by different workers[114,115], the basic structure of which was proved by the elegant work of different groups of workers[116-118], was found to show activity against leukemia 82 in experimental animals[119].



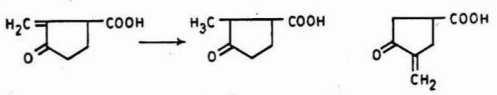
XLIV XLV



XLVI

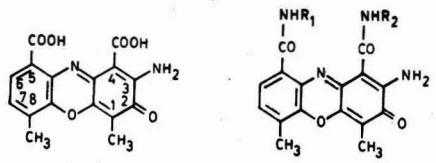
More work should be done with this antibiotic (XLVI) to prove its antitumour activity.

Sarkomycin (XLVII), a relatively unstable antibiotic isolated by Umezawa *et al.*[120] and purified by Hooper *et al.*[121], was found to be effective against Ehrilch ascites tumour in mice[122]. The antitumour activity of sarkomycin is probably due to the presence of 1:4-conjugated system which acts as an alkylating agent. However, as this substance (XLVII) bears very little resemblance to other types of anticancer agents, much more work on this line should be done as to throw a definite mechanism of its reaction in the biological system. The hydrogenated product (XLVIII) of sarkomycin has also antitumour activity although the antibacterial properties are lost. Another advantage of sarkomycin as antitumour agent over others is its considerably low toxicity. The isomeric compound, 5-methylenecyclopentanone-3-carboxylic acid (XLIX), also possesses anticancer activity[123].



XLVII XLVIII XLIX

The actinomycins are a group of antibiotics having a common chromophoric group, 3-amino-4,5-dicarboxy-1,8-dimethyl-2-phenoxazone (L), although they differ in the composition of their polypeptide side chains (R_1 and R_2 represent the polypeptide side chains in structure LI).



L LI

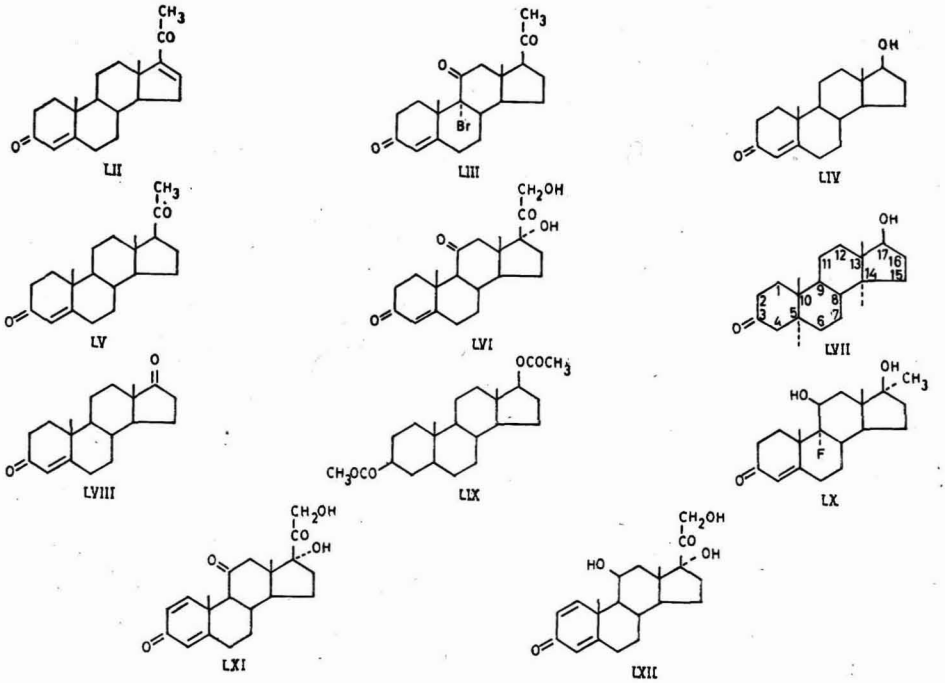
Actinomycins C and D both have carcinolytic action on several transplanted tumours. They are all highly toxic. It has been observed by Foley[124] that actinomycin D is an antimetabolite of pantothenic acid in a microbiological system, but its effect in mice could not be reversed by the addition of pantothenic acid.

Hormones as Anticancer Agents

Hormones are substances which are secreted internally by particular organs and are carried by blood or lymph to other organs for the control of growth and activity. It is quite natural to suppose that the growth of abnormal cells cannot be independent of normal cells, but must retain some characteristics of the parent tissues from which they have been originated. As has been said before, an ideal antitumour agent will be that compound which will only be able to destroy the cancer cells without affecting the normal cells. Huggins[125,126] first pointed out that the cancer of sex organs could be controlled by bilateral adrenalectomy. Androgen control therapy, by means of castration and application of estradiol ester and other synthetic estrogens, has some effect on metastatic carcinoma of the postrate and breast of the male[127]. The anticancer activity of Δ^{16}-progesterone (LII) has also been reported by Iglesias[128]. 9α-Bromo-11-oxoprogesterone (LIII) was tried in breast cancer, testosterone (LIV), progesterone (LV) and cortisone (LVI) have been used in lung cancer. Testosterone as propionate is effective against breast cancer. Other androgens, though not so successful as testosterone propionate, administered in the treatment of breast cancer are dihydrotestosterone[129] (LVII), 4-androstene-3,7-dione (LVIII), androstane-3β,17β-diol acetate (LIX) and 9α-fluoro-11β-hydroxy-17α-methyl testosterone[130] (LX). The adrenal or adrenocorticotropic hormones, ACTH, and cortisone have limited therapeutic activity in leukemias and lymphomas. Δ^1-Dehydrocortisone (LXI), Δ^1-dehydrohydrocortisone (LXII) and their fluoro analogues show promise in the treatment of various types of cancer.

Miscellaneous Antitumour Agents

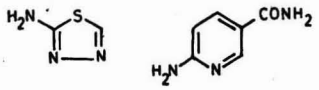
An enormous number of antitumour agents having a variety of structural features have been prepared and tested in different types of cancer, but, owing to their toxicity, their application as antitumour agents is very limited. The mode of reaction of these agents is not yet clearly understood. However, a brief review of some of the important



anticancer agents of this group will be discussed hereunder.

Urethane[131] (ethyl carbamate, $RNHCOOC_2H_5$, where R = alkyl or aryl groups), probably the most widely used drug in this group, is effective in Walker carcinoma 256 and in chronic granulocytic leukemia[132]. Out of a number of carbamates which have been tested in experimental animals, only a few N-phenylcarbamates[133] have shown some promising results.

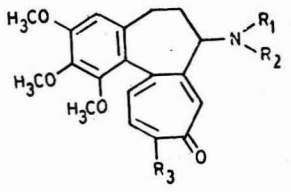
A few derivatives of 2-amino-1,3,4-thiadiazole (LXIII) have been tested in experimental animals with some success[134,135]. It has been further observed that niacinamide reverses the effect of these drugs[136]. 6-Aminonicotinamide (LXIV) was also found to inhibit the growth of carcinoma 755 and the activity of which could be reversed by the addition of niacinamide.



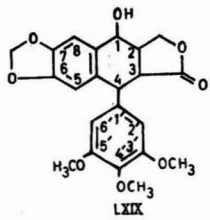
Attention has also been directed towards plant sources for the possibility of getting active principles with potential antitumour activity. Colchicine (LXV), a plant product, was tried, but it had limited application in the treatment of neoplastic diseases because of its high toxicity. Some of the derivatives of colchicine, viz. deacetylcolchicine (LXVI), N-methyldeacetylcolchicine (LXVII) and N-deacetylthiocolchicine (LXVIII), have been found to be effective in several cases of chronic myeloid but without any effect in acute myeloblastic or chronic lymphatic leukemias[137,138]. N-Methyldeacetylcolchicine (LXVII) is about forty times less toxic than colchicine (LXV).

Podophyllotoxin (LXIX), another plant product obtained from podophyllin resin, does not show promising result owing to its high toxicity[139-142]. Colchicine and its derivatives damage the cell at the metaphase, whereas podophyllotoxin inhibits cell division at the prophase stage of the mitotic process.

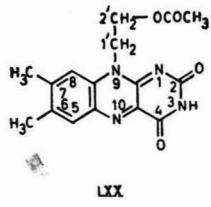
Some vitamin antimetabolites, other than antifolics, have also been prepared in the hope of getting selective antitumour agents. The clue for such a drive was derived from the observation that the concentrations of certain vitamins, specially vitamins of B-group, are lower in cancer cells than in normal cells. These vitamin antimetabolites may be presumed to act as enzyme inhibitors, since the vitamins of the B-group generally function as



LXV colchicine, R_1=H; R_2=$COCH_3$; R_3=OCH_3
LXVI deacetylcolchicine, R_1=R_2=H; R_3=OCH_3
LXVII N-methyldeacetylcolchicine, R_1=H; R_2=CH_3; R_3=OCH_3
LXVIII N-deacetylthiocolchicine, R_1=H; R_2=H; R_3=SCH_3



LXIX



LXX

coenzymes of specific enzyme systems. Some of the vitamins of B-group for which antagonists have been prepared are riboflavin[143], vitamin B_6[144] and vitamin B_{12}[145]. A riboflavin analogue, 6,7-dimethyl-9-(2'-acetoxyethyl)-isoalloxazine[146] (LXX), has been found to possess antitumour activity in experimental animals.

The application of isotopes in cancer chemotherapy has been studied by various workers in the hope of destroying the abnormal tissues selectively without causing any deleterious effect to normal cells. The idea behind application of such a therapy is that the labelled elements (isotopes) will certainly possess the same characteristics of the parent elements and will follow the same principle of distribution in the system as the non-labelled elements and the radiation emanating from these isotopes at the site of the abnormal tissues may either damage the cancer cells or inhibit their further growth without causing any deleterious effect to the growth of normal cells very much. I-131, K-40, Na-24, P-32 and Au-192 have been tested against specific tumours with some success.

As has been already pointed out, the problem of finding an ideal chemotherapeutic agent for different types of cancer is a very difficult one with our present limited knowledge concerning the essential differences which might exist between normal and abnormal cells. It is to be fervently hoped that the secret of the nature of neoplastic diseases will be revealed sooner or later and will enable the experimentalists to find out more selective antitumour agents.

In conclusion, the author would like to add that the subject has not been dealt with here in an exhaustive way, nor is it possible to describe the research work of innumerable workers in this field within the purview of such a short article, for which excellent books have already been written by eminent scientists. The main purpose of this article is to present a general idea concerning the development in chemotherapy of cancer to the research workers, who wish to study further the problem of finding out ideal chemotherapeutic agents capable of eradicating this heinous and deadly disease.

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The Chemistry of Noble Gases*

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SINCE the discovery of noble gases, at the turn of the century, scientists held the view that these elements are incapable of forming normal chemical compounds and this notion was supported by the stable electronic octet theory of valence. This view was further strengthened by the failures of a few serious attempts to prepare normal chemical compounds of these elements[1]. However, the belief in the invulnerability of the noble gases to any chemical reaction was shattered with the discovery of the tetrafluoride of xenon[2,3]. This discovery is all the more startling in that xenon tetrafluoride can be prepared very easily and is remarkably stable at room temperature. Since then about 50 papers have been published dealing with the experimental and theoretical aspects of the chemistry of these elements, of which a few only have been referred to here.

The pioneering observation was made by Bartlett[4,5] while investigating the remarkable oxidizing property of the gas, platinum hexafluoride. He was able to oxidize molecular oxygen and the compound was identified as $O_2^+[PtF_6]^-$. Since the first ionizing potential of molecular oxygen, 12·2 eV., is the same as that of xenon, he worked upon the possibility of isolating the analogous compound containing oxidized xenon and was successful in preparing $Xe^+[PtF_6]^-$ at room temperature. Following this lead, Claassen *et al.*[2] observed that more than one mole of hexafluoride was consumed per atom of xenon (Bartlett assumed a combining ratio of 1:1) and that a heterogeneous product was formed. This suggested that the hexafluoride was at least, in part, acting as a fluorinating agent and that fluorides of xenon might have been formed. This led to the discovery of simple fluorides of xenon. Thus it was possible to integrate Gr. VIIIA ('inert' gas elements) in the periodic table with other groups, which so long occupied an isolated position because of their presumed non-reactivity.

Among inert gas elements, fluorides of Xe, Rn and Kr have been isolated and the presence of oxyfluorides and a trioxide of xenon has been demonstrated. So far no chemical compounds containing such strong oxidizers like chlorine have been prepared.

Methods of Preparation and Chemical Properties

The different methods of preparation of fluorides of noble gases can be subdivided into four classes:

(a) *Thermal process*[2,3,6-10] using high temperature and pressure and an excess of fluorine. Ratio of fluorine to xenon may vary from 4 : 1 to 20 : 1.

(b) *High voltage electric discharge*[11] — Xenon tetrafluoride has been prepared from elements (F-Xe ratio being 2 : 1) by this method; the presence of XeF_2 has also been demonstrated by altering the ratio of F-Xe to 1 : 1. Its advantages over the usual thermal methods are that it is continuous, quantitative and excess of fluorine is not required.

(c) *Method avoiding the use of elementary fluorine*[12] — This method uses high voltage discharge through Xe and CF_4. Principal compound formed is XeF_2.

(d) *Matrix isolation technique* — Thermodynamically unstable KrF_2 (the only stable fluoride of Kr is KrF_4; it has been prepared by method B[12]) has

*A brief report of the Conference on Noble Gas Compound, held at Argonne National Laboratory on 22 and 23 April 1963, which appeared in *Science*, **141** (1963), 61.

been successfully isolated and identified by Turner and Pimentel[13] by this method, which involves the photolysis of fluorine suspended in a solid mixture of argon and krypton at 20°K. held upon a solid CsI window. This is one of the recently developed methods which makes possible the identification of chemical compounds of transitory existence. Among the methods of identification of unstable compounds time-of-flight mass spectrometry played an important part. It first revealed[3] the presence of XeF_2 and $XeOF_4$. Other method includes electron spin resonance technique at low temperature (77°K.) in XeF_4 crystal[14] irradiated with Co^{60} gamma source. Odd electron species XeF is the compound identified by this technique which is consistent with observations of flash photolysis experiments in gaseous mixtures of xenon and fluorine !

The existence of XeF_8 and XeF_5 has also been postulated, but they are still in the realm of speculation. The presence of chemical compounds of xenon that has been confirmed include XeF_2, XeF_4, XeF_6, XeF and $XeOF_4$. Of the krypton compounds KrF_4 and KrF_2 are known up till now.

Though the existence of radon fluorides (mainly RnF_2) has positively been established[3,7], it requires elaborate shielding arrangements to prepare these compounds in some quantity.

The only compound of xenon not containing fluorine is XeO_3. It is extremely explosive and is formed[15] by the hydrolysis of XeF_6. Its structure has also been determined by X-ray method[15] and found to be trigonal pyramid similar to its electron analogue — iodate ion. However, the absence of any hydrogen bonding makes the formulation $HXeO_3$ implausible in spite of its similarity with iodic acid.

The hydrolysis reaction of XeF_4 and XeF_6 is complex and the nature of the products obscure[3]. The solid[16] remaining after hydrolysis detonates on warming *in vacuo* above 30-40°C.

In acid solutions, the most stable species obtained from XeF_6 or XeF_4, after disproportionation, appears to be a xenon compound with the oxidation number of 6. The oxidation number is determined by reaction with reducing reagents such as titration with iodide ion[17]. In alkaline solution, on the other hand, the predominant species obtained from the hydrolysis of XeF_6 seems to contain xenon with the oxidation number of 8.

In anhydrous hydrogen fluoride, XeF_4 is sparingly soluble[3] with no reaction or ionization. This precludes any ionic mechanism in the hydrolysis reaction of XeF_4. However, XeF_2 is readily soluble in anhydrous hydrogen fluoride with some ionization as is expected from quantum mechanical calculations[18] showing that the charge distribution in XeF_2 should resemble ionic compounds and the solution of XeF_2 in high dielectric constant solvents should be ionic. XeF_6 is highly soluble with extensive ionization.

Electronic Theories of Bonding and Structure

After the first shock of the synthesis of normal chemical compounds containing noble gases has worn off, chemists are in agreement that the elucidation of the structures of these compounds will not require the introduction of new concepts in quantum chemistry. In fact, it was pointed out by Pimentel[19] as early as 1951 using the existing theories that the existence of 'inert' gas-halogen compounds is possible.

However, the conventional bonding scheme employing sp hybridization is not applicable to XeF_2 from energy considerations. Other suggestions for binding in these compounds include instantaneous electron correlation effects[20,21], but it is not evident that this scheme will give bonding at all[18].

The important question in elucidating the bonding problem is to know whether $5p$ or $5d$ atomic orbitals of xenon are involved in the bonding in xenon fluoride compounds, apart from the use of the $6s$ shell. The possible use of the $6s$ level for bonding is rejected by Argon and Levy[22] who point out that the Xe–F bond distance is too short ($2{\cdot}00 \pm 0{\cdot}01$ A.) for this to occur. The linear structure of XeF_2 determined by neutron[22] and X-ray diffraction[23] indicate the favoured use of the $5d$ level, because the principal and interaction force constants differ markedly from those of the electronic analogue ICl_2^- ion, which has been shown to have essentially one-electron bonds[24]. On the other hand, Pimentel and Spratley[25] do not share this view. They contend that the bonding scheme in the trihalide ions as proposed by one of them[19] is applicable to the 'inert' gas-halogen compounds and they have been largely supported by others[18,26-28] who have all particularly emphasized the correlation between interhalogen compounds and fluorides of xenon in respect of their structure, stability and nature of binding. Jortner *et al.*[18] proposed to describe the bonding in the hexafluorides in terms of delocalized molecular orbitals formed mainly by the combination of $5p\sigma$ atomic orbitals of xenon and $2p\sigma$ atomic orbitals of fluorine. Pitzer[28] elaborates the significance of interhalogen compounds in relation to inert gas-halogen compounds (e.g. the relation between BrF and BrF_5 is analogous to that between Xe and XeF_4). He also emphasizes the dependence of the stability of fluorides of rare gases primarily on the ionization potential of the central atom. It has been pointed out by all these workers that there is little likelihood of d orbital participation in the bonding.

XeF_4 crystalizes either in monoclinic or orthorhombic symmetry[3]. The crystal structures of XeF_2, XeF_4 and XeF_6 have been extensively investigated by X-ray[29], neutron diffraction[30], infrared[3] and far ultraviolet spectra[31]. The assemblage of fluorines in XeF_4 molecule is square planar around xenon and the precision of the shape of assemblage of squares in the crystal is second to none. The linear shape of the XeF_2 and the crystal structure of the solid have been well established. The average XeF bond distance in the planar XeF_4 molecules is 1·953 A. while that in linear XeF_2 is 2·00 A. NMR spectrum of XeF_4 in anhydrous HF has revealed the retention of the square-planar structure of the molecule in solution. The compound is remarkably stable in solution[32].

On thermodynamic considerations XeF_4 and XeF_2 are more stable than BrF_3 and BrF_5. The bond energy per Xe–F bond in XeF_4 is 30 kcal.[33].

The structure of XeF_6 is particularly interesting and crucial in the sense that exact determination of the structure will end the controversy between the alternate theories of bonding. Thus if *d* orbitals are used we should have a 14-electron (possibly distorted) pentagonal by pyramidal arrangement of electron pairs with one lone pair; on the other hand, if only *p* orbitals are used a regular octahedron should be formed[34]. Unfortunately, however, the structure of XeF_6 in either solid or vapour phase has not been established. The most complete analysis of the scanty infrared and Raman data available appears to reject the symmetrical octahedral structure for XeF_6. However, analysis of some portions of the data is subject to alternate interpretation. For example, an absorption band at 520 $cm.^{-1}$ has been observed and has been attributed to XeF_6 molecule by Smith[24], whereas others are inclined to believe that this may be due to other species, e.g. an odd electron-free radical XeF_5. It is expected that the discrepancy will be soon removed.

Conclusion

Few discoveries in recent times have created such wide interest among chemists as the discovery of chemical compounds of ' inert ' gases. One is really astonished at the remarkable ease with which stable normal valence bond compounds of xenon of fluorine can be prepared. As Abelson[35] has remarked, " For perhaps 15 years, at least a million scientists all over the world have been blind to a potential opportunity to make this important discovery. All that was required to overthrow a respectable and entrenched dogma was a few hours of effort and a germ of skepticism."

The author wishes to thank Prof. S. R. Palit and Dr P. Mukerjee for many helpful discussions.

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REVIEWS

STRANGE PARTICLES by R. K. Adair & E. C. Fowler (Interscience Publishers, a Division of John Wiley & Sons Inc., New York), 1963. Pp. viii+151. Price $ 4.75

As the authors state in the preface, the purpose of this book is to summarize the important properties of the strange particles in the context of basic theoretical ideas. The selection of the subject matter and the presentation is such that it will have appeal to the newcomer in the study of elementary particle physics. Even the experts would value this book as a neat collection of important results and analysis of some of the basic experiments.

Apart from the introduction, there are four chapters entitled Properties, Strong interactions, Weak interactions and Formalism. The introduction consists mainly of a historical sketch of the development of the strange particle physics since almost two decades ago. In the second chapter, the concepts of strangeness, spin, parity and isotopic spin are explained on the basis of experiments and basic formalism is introduced. The chapter on strong interactions introduces the language of dispersion diagrams without, of course, going into any detail and explains quite successfully the dominant mechanism of the better understood strong processes. A somewhat sketchy treatment of resonances is also given, which is inadequate and outdated. In the fourth chapter, the main features of weak processes of the strange particles are discussed. The fifth chapter is an excellent collection of formulae and formal results of regular use in the study of elementary particle physics.

This book achieves the object put forth in the preface creditably. The style is lucid and easy to understand, keeping mathematics and theoretical sophistication to the minimum. It is strongly recommended to all those who are entering on a research career in elementary particle physics.

GYAN MOHAN

THERMOELASTICITY by W. Nowacki (Pergamon Press Ltd, Oxford), 1963. Pp. ix+628. Price £ 6 6s.

One may take up any theory in continuum mechanics or even in any other field to study, but the ideas are not well fixed in mind unless one works out some problems illustrating the theory. Several new aspects of the theory become clear only on analysing the specific problems in it. The present book serves this purpose well. After taking stock of all the necessary basic equations of thermoelasticity in the very first chapter, the author goes to discuss various types of problems, occurring in the theory. These are as follows: (i) stationary three-dimensional thermoelastic problems; (ii) quasi-static and quasi-stationary spatial thermoelasticity problems; (iii) dynamic effects due to the action of a non-stationary temperature field; (iv) dynamic problems of coupled temperature and strain fields; (v) stationary plane problems; (vi) quasi-static and quasi-stationary two-dimensional thermoelastic problems; (vii) two-dimensional dynamic thermoelastic problems; (viii) thermal stresses in plates; and (ix) thermal stresses in shells. The main methods employed in solving the problems consist of (a) Galerkin's stress functions, (b) Maysel's method, (c) Green's functions and (d) integral transforms of Fourier, Hankel and Laplace.

Solutions, though explicitly given, are based upon the assumptions of small strain, linear stress-strain laws, isotropic and homogeneous bodies, elastic constants being independent of temperature. These assumptions, no doubt, make the solutions applicable only within certain ranges of temperature and deformations. But one has to be guided by the practical side as well. The linear theory appears to be more in agreement with the experimental observations than any other theory. Non-linear thermoelasticity is obviously not within the scope of the present book. None the less, the author has included, in the last two chapters, some of the recent researches on thermal stresses in linear viscoelastic bodies and in anisotropic bodies. The book is more suitable for applied mathematicians and engineers rather than those who go deep into the physics of the thermoelastic phenomena.

A. S. GUPTA

CLASSICAL ELECTROMAGNETIC THEORY by Nunzio Tralli (McGraw-Hill Book Co. Inc., New York), 1963. Pp. ix+308. Price $ 9.95

This is intended to be a text-book for graduate students. It tries to explain " the physical concepts of electricity and magnetism, describing the mathematical formalism and presenting examples of both ideas and methods involved ". It is not an original or a critical book but a compilation which will be useful to students and teachers. The emphasis throughout is on mathematical description and the experimental checks are rarely, if ever, mentioned. The chapters usually end rather abruptly in mathematical formulae without explanation of the significance of the results they imply. After reading the book, a student is apt to get the feeling that physics is no more than a branch of mathematics.

There are some places where the mathematical statements made in the text should be more carefully worded or explained. For example, while solving Poisson's equation, $\nabla^2\phi\ (x_1', x_2', x_3') = -\rho\,(x', x_2', x_3')$, the boundary condition mentioned is that " ϕ and $\vec{\nabla\phi}$ both should vanish as (x_1, x_2, x_3) approaches $\pm\infty$ ". This is meaningless unless one specifies the origin of the coordinate system in relation to the charge distribution. On the same page, description of the second term in Eq. (1.73) as arising from sources outside the volume concerned needs explaining. The reason why the solid angle integral, $\int d\omega$, is put equal to zero on page 44 should be further elaborated. The concept of causality is so important in physics that it deserves greater elaboration than its brief mention on page 170 to discard the advanced potentials.

There are some minor printing errors, but none is serious. The exercises at the end of the chapters are instructive.

VACHASPATI

PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON CRYSTAL LATTICE DEFECTS, Tokyo, September 1962. *J. phys. Soc. Japan*, Vol. 18, Supplements (Physical Society, Japan), 1963. Pp. Suppl. 1: ii+200; Suppl. 2: iii+358; and Suppl. 3: iii+375

As is obvious from the title, these are the proceedings of the International Conference on Crystal Lattice Defects, held in Japan in September 1962, published in three volumes as three supplements to the *Journal of the Physical Society of Japan*. The first supplement contains 34 papers presented in the first part of the conference, Symposium on Mechanical Aspects of Lattice Defects, held at Tokyo on 3 and 4 September 1962. There are 9 papers on motion of dislocations, 7 on work hardening and 18 on internal friction. The supplements 2 and 3 are the proceedings of the second part of the Conference on Crystal Lattice Defects, held at Kyoto during 7-12 September 1962. The Kyoto conference was divided into three sections. Sixty-nine papers, presented at the first section 'Fundamental properties of lattice defects', and two evening lectures are given in the second supplement. The lectures are 'Field ion microscopy of the defect structure of metal crystals' by E. W. Muller and 'The study of crystal imperfections in thermal conductivity measurements' by K. Mendelssohn. The papers are divided over eight sessions: 9 papers are on magnetic resonance and optical studies of lattice defects; 6 papers on electrons and phonons in imperfect lattices; 8 papers on scattering of electrons and phonons by lattice defects; 4 papers on equilibrium among defects in compounds; 3 papers on impurity conduction and energy levels of defects in semiconductors; 13 papers on formation and migration of point defects; 19 papers on colour centres and luminescence; and 7 papers on observations of lattice defects. Thirty papers presented at the second section 'Interaction between lattice defects' and 42 papers at the third section 'Production and annealing of lattice defects' are included in the third supplement. The papers are divided over seven sessions: Interaction between defects in metals I (16 papers); Interaction between defects in metals II (7 papers); Interaction between defects in non-metals (7 papers); Radiation production of lattice defects (10 papers); Radiation effects in non-metals I (9 papers); Radiation damage in and recovery steps in metals (11 papers); and Radiation effects in non-metals II (12 papers). As the number of papers is very large (175 papers), it is not possible to discuss the papers in any detail. A very large number of outstanding papers are by the Japanese workers, and their papers on interactions between defects in metals are particularly important.

Brief mention may be made of some of the more important papers here. At the Tokyo symposium, a very detailed experimental paper on the motion and multiplication of dislocations in copper crystals is by F. W. Young (Jr). Both annealed and neutron irradiated crystals were studied. A. Seeger's paper has given a detailed account of the extensive work done on the mechanical properties of FCC single crystals at Stuttgart. J. S. Kochler, M. De Long and F. Seitz have given a very interesting paper on the kinetics of the formation of divacancies and vacancy clusters, and on the equilibrium ratio of single and divacancies. The authors have discussed in detail examples where mathematics can be made relatively simple and have pointed out other problems which are more difficult. G. D. Watkins has described detailed electron paramagnetic resonance studies of silicon irradiation by 1·5 MeV. electrons. Surprisingly his results yield a value of 0·33 eV. for the activation energy for the migration of a single vacancy where activation energy for diffusion in silicon is about 4 eV. V. S. Vavrlov, USSR, has also given a paper on the defects introduced in silicon single crystals by electron and neutron irradiation. Several interesting papers were presented on the recovery stages in noble metals. Among the papers presented on colour centres and luminescence, mention may be made of a very interesting paper by F. Luty and H. Pick of Stuttgart, Germany. They constructed configuration coordinate diagram for the F and the Fa centre from the experimental data on optical absorption and fluorescence emission, and have derived much useful information. F. Okamoto and A. B. Scott, USA, have discussed the effect of impurities on the growth and bleaching rates of F centres. The mechanism for resonance energy transfer in the absorption of light by a pair of neighbouring ions in a crystal has been discussed by D. L. Dexter, USA.

The material presented in these three volumes gives some idea of the vast amount of experimental and theoretical work being done in this field and the promise that future studies hold out for both academic understanding and practical applications of lattice defects.

S. C. JAIN

MICROWAVE TUBES AND SEMICONDUCTOR DEVICES by G. D. Sims & I. M. Stephenson (Blackie & Sons Ltd, London), 1963. Pp. xxii+388. Price 75*s*.

The aim of the authors, as stated in the preface, had been to present an 'up-to-date and readable' survey of the theory and applications of microwave devices concentrating on "physical explanation rather than on introduction of formulas which are often of little practical use". A perusal of the volume shows that they have achieved a large measure of success in this venture without sacrificing the essential core of the mathematical theory. The success is heightened by the fact that they have tried to cover in a single volume of modest size the entire domain of microwave devices including, in addition to the vacuum and semiconductor devices, those involving quantum electronics, viz. masers and lasers. A short historical review in the introduction is followed by Chapter 1 covering the basic physical phenomena like energy exchange and space charge waves. Design of electron guns and maintenance of electron beams are discussed in Chapter 2. Velocity modulated tubes are dealt with in Chapters 3 and 4. The next three chapters are devoted to considerations of tubes based on travelling wave

interaction — Chapter 6 dealing exclusively with the important topic of slow wave structures. Magnetrons and related tubes are then discussed in a separate chapter owing possibly to historical reasons. This, no doubt, creates a little confusion about the magnetron amplifier. Parametric devices are discussed in Chapters 9 and 10 — the latter being concerned solely with the cyclotron wave device which is *ipso facto* Adler's tube. A hurried survey of masers and lasers is presented in Chapter 11. The next chapter is an outline of the semiconductor devices including the point contact diode, the mesa transistor and the tunnel diode. Chapter 13 comprises 6 tables giving comparative studies of the various classes of devices. The volume concludes with 8 appendices giving a fairly comprehensive glossary, certain mathematical derivations, values of a few physical constants and description of special types of cathodes. Printing and general get-up are in keeping with the reputation of the publisher. The book is expected to cater well for the needs of the undergraduate student and to provide for the intending specialist a helpful foothold on the physical principles of microwave devices.

S. DEB

NUMERICAL SOLUTION OF ORDINARY AND PARTIAL DIFFERENTIAL EQUATIONS by L. Fox (Pergamon Press Ltd, Oxford, and Addison-Wesley Publishing Co. Inc., Reading, Massachusetts), 1962. Pp. ix +509. Price $ 10.00

This advanced-level text or reference work is based on material presented at a Summer School for representatives of industry, government, universities and technical colleges, held at the University Computing Laboratory, Oxford, England, in September 1961. It is essentially a presentation of the material, both theoretical and practical, needed for the numerical solution of all types of problems involving ordinary differential equations, integral equations and partial differential equations of quasi-linear form. Throughout the book electronic computers have been kept in mind. As stated in the preface, the book is written " for scientists who have problems to solve, and who want to know what methods exist, why and in what circumstances some are better than others, and how to adapt and develop techniques for new problems ". Long and difficult proofs of a purely mathematical interest are, therefore, often only sketched; on the other hand, great importance is given to the practical aspects of the technique " from the standpoints of accuracy, convergence and stability as well as ease of coding and convenience of machine computation ".

The book is divided into four parts. The first three parts, constituting the expository sections, include modified versions of some of the material found in the standard books, but the authors have tried to include, either fully, briefly or by reference, all the latest and important facts and techniques, and have indicated what is not known and what current research is in progress.

Part I, dealing with ordinary differential equations, extends over 141 pages and has ten chapters on differences, Runge-Kutta methods, prediction and correction, stability, boundary-value problems, eigen-value problems, one-dimensional Schrödinger equation, accuracy and precision, Chebyshev approximation, methods of Lanczos and Clenshaw for Chebyshev solution of ordinary differential equations.

Part II, with 58 pages, is devoted to integral equations and has six chapters on Fredholm equations, equations of Volterra type, singular and non-linear equations, integro-differential equations, Roothaan's procedure for Hartree-Fock equations.

Part III, with 93 pages, is an introduction to partial differential equations and has eight chapters. These deal with general classification, difference methods for hyperbolic equations (in two variables), parabolic and elliptic equations in two dimensions (finite-difference methods, direct solution, iterative solution, singularities).

While the first three parts are largely the contribution of Dr Fox and Dr Mayer, the fourth part, which deals with some practical problems of the greatest difficulty and complexity, " which tax not only the best machines but also the best brains ", is the contribution of specialists. This part has 79 pages and the twelve chapters deal with elliptic equations in nuclear problems, equations of one-dimensional unsteady flow (solution by characteristics and by finite-difference methods), quasi-linear problems in more than two dimensions, linear transport equation in one and two dimensions, Monte Carlo methods, some problems in plasma physics, numerical weather prediction.

The value of the book is greatly enhanced by the references given for the first three parts and the chapter-wise references for the fourth part. The book gives a remarkably lucid, comprehensive and up-to-date survey of the field, and is a most valuable addition to the literature on numerical solutions.

SURYA PRAKASH

MECHANICAL VIBRATIONS by Austin H. Church (John Wiley & Sons Inc., New York), Second Edition, 1963. Pp. xix+432. Price $ 12.00

The subject of mechanical vibration has gradually developed into such a broad field that a time has now come to separate out the topics which will form the subject matter for an introductory course, and leave the more complex ones for advanced studies. The book meets this requirement. It is an excellent introductory of the transient and steady state behaviour of simple vibrating systems, with special emphasis on application of the use of phase-plane diagrams, Laplace transforms and mobility methods. The classical method has also been presented very clearly. The mathematical background of the reader is presumed to be limited and, therefore, each step of mathematical analysis has been carefully explained. The physical aspect of the results arrived at has been successfully brought out by elaborate discussions.

The text material begins with an introductory chapter dealing with scope, definitions, derivation of simple mathematical relations, etc. The following headings of the remaining eight chapters give a fairly good idea of the material covered in the book: Undamped free and transient vibrations — single degree freedom; Damped free and transient vibrations — single degree freedom; Steady state forced vibrations — single degree freedom; Introduction to Laplace transformation; Electrical analogies and mobility;

Two degrees of freedom; Multimass lumped systems; and Distributed systems.

Many solved examples are presented clearly by many illustrative diagrams clarifying the procedure and application of the results. These solved examples have also been used in places for extending the analysis. Moreover, each chapter contains a list of references and several unsolved problems suitable for assignment. A further bibliography is added at the end of the book giving a partial list of books on vibration and shock.

The topics not included in the book are: non-linear vibrations, noise and random vibrations, plates, shells, membranes and general case of self-excited vibration. The reviewer feels that the reference to stick-slip phenomenon could have been safely omitted to be studied along with general case self-excited vibration. Too simplified an explanation of the stick-slip is rather misleading. There are some printing slips which have crept in. The reference on page 218 is not up to date; a second edition of the book under joint authorship has appeared in 1959.

The book is a useful one for undergraduates.

B. M. BELGAUMKAR

DIGITAL COMPUTER TECHNOLOGY AND DESIGN: Vol. I — MATHEMATICAL TOPICS, PRINCIPLES OF OPERATION AND PROGRAMMING; Vol. II — CIRCUITS AND MACHINE DESIGN by Willis H. Ware (John Wiley & Sons Inc., New York), 1963. Pp. Vol. I, xviii+245; and Vol. II, xx+536. Price Vol. I, $ 7.95; and Vol. II, $ 11.75

The book under review is an introductory text in the field of digital computer techniques in two volumes. Vol. I deals with mathematical topics, principles of operation and programming. Vol. II covers the circuits and machine design. The presentation is highly suitable for those who are new to the field. The material presented in each chapter is built up from the basic principles. The book is a self-contained volume, and a reader going through it should be able to get a good insight into the basic principles underlying the computer technique.

Towards the end of Vol. I, the author initiates the reader into the technique of programming. A major omission in this chapter is language programming. With the advancement of efficient and easy-to-use languages, most of the machine programming is being done in one of these. An introduction to the structure and use of these languages would have been very useful.

The chapter on reliability deserves special attention. This is a very important aspect of the digital techniques and is overlooked in most of the texts on the subject. Normally, however, reliability is more of a designer's criterion rather than a user's one. The author deals with this aspect of the problem in Vol. II. The rest of the volume is devoted to a rather detailed discussion of computer elements and basic organizational principles.

A certain amount of redundancy is inevitable in a book of this nature. It probably would have been possible to treat the subject matter presented in a more concise fashion, but then much of the easy readability of the book would have been lost.

S. K. BASU

MULTILINEAR ANALYSIS FOR STUDENTS IN ENGINEERING AND SCIENCE by G. A. Hawkins (John Wiley & Sons Inc., New York), 1963. Pp. xiv+219. Price cloth bound, $ 6.50; paper bound, $ 2.95

With the rapid advance in science and technology self-study books in basic sciences have become a great necessity. Vectors, matrices and tensors in linear algebra are extensively used in all scientific and engineering disciplines. A large number of texts have been written on these subjects. The present one is a useful self-study edition written by an engineer. It presents a simplified treatment without going deep into the rigour of the methods involved. It also clarifies and explains in detail a number of difficulties encountered by the beginner. Each chapter ends with a number of useful examples and references for advanced reading.

B. R. SETH

PARTIALLY ORDERED ALGEBRAIC SYSTEMS by L. Fuchs (Pergamon Press Ltd, Oxford), 1963. Pp. ix+229. Price 50*s*.

This monograph of about 220 pages packs in a lot of material concerning partially ordered groups, rings, fields and semigroups, which till now were scattered among many journals, in original papers. For workers in the field the book is bound to be a great boon as it will help to get relevant material on these topics without considerable search.

The interest in the ordered algebraic systems has been great in recent years. Problems of extending a partial order to total orders, of representing partially ordered algebras as subalgebras of special types, like vector ordered algebras, or in terms of lexicographic sums, or in terms of valuations, all these have been tackled by different workers.

This book covers most of the important results in its three parts: Partially ordered groups, Partially ordered rings and fields, and Partially ordered semigroups. Under each part, after a chapter on preliminaries, fully ordered structures and lattice ordered structures are dealt with. The extensibility question (of a partial order to a full order) is also treated in the first two parts.

Notes on references in the text give supplementary information on related results which are not included. The bibliography is extensive, and a list of problems adds to the value of the book.

The book is bound to be in great demand among workers in this field.

V. S. KRISHNAN

THE PERFECT GAS by J. S. Rowlinson (Pergamon Press Ltd, Oxford), 1963. Pp. xii+136. Price 30*s*.

It is very pleasing to note that a comprehensive effort has been made to put together the up-to-date knowledge on topics which are on border of physical chemistry and chemical physics in the form of an international encyclopaedia. The editors-in-chief have taken a wise but nevertheless an essential step in grouping the subject matter in different topics, each having its own editor. In topic ten, the fluid state, the volume five on *The perfect gas* written by Prof. J. S. Rowlinson is under review here.

The author has done an excellent job in collecting and arranging the information on the subject in a

limited space of 135 pages. This is obviously a very hard job on a subject which is as old as the knowledge of science and on which a large amount of work has been done. No unique arrangement for such a limited space is possible, and the author has presented the matter in six different chapters maintaining sequence of thought and clarity of presentation.

In the first chapter, the important thermodynamic relations relevant to the theoretical and experimental study of a perfect gas have been briefly summarized. The second chapter deals with the experimental methods of determining the heat capacities of gases at low and moderate pressures. One of the greatest assets of statistical thermodynamics is its competence to be able to predict the macroscopic properties of gases. Such calculations are described in the third chapter and the theoretically computed values have been compared with the experimental results for a few actual systems. The properties of a perfect gas mixture are discussed in the fourth chapter and a comparison of the observed and calculated values is presented. Similar discussion is also given for the reacting gases. In the fifth chapter, the topics of molecular collision, propagation of sound waves, classical absorption of ultrasonic waves and relaxation of internal degrees of freedom of polyatomic molecules have been briefly dealt with. The behaviour of a flowing gas, which is very important for a variety of problems of fluid dynamics, forms the subject matter of the sixth chapter.

This nicely bound and printed volume on the whole knits the subject matter into a very elegant readable form. Each chapter is nicely concluded with a list of references which forms a very valuable and adequate reservoir of information for postgraduate and research students in the beginning.

It is usually unfair to criticize an author for what he did not do. This is particularly true when the space available is limited. But this book could have been still more useful if the author had appended a complete up-to-date bibliography as an aid to research workers. This is particularly important for in a few topics the present knowledge is more advanced than the author could bring up to.

S. C. SAXENA

PARTICLE SIZE: MEASUREMENT, INTERPRETATION AND APPLICATION by Riyad R. Irani & Clayton F. Callis (John Wiley & Sons Inc., New York), 1963. Pp. 165. Price $ 7.50

Physicists and industrial hygienists have contributed much to the development of the subject of particle size measurement in the early decades of this century. However, the subject has assumed an importance of its own during the last two or three decades, mainly from the fact, that in modern technology, material in a powdered form is produced and consumed in enormous quantities.

The classical methods of particle size measurement by sedimentation, microscopy and sieving have been made in recent years more rapid and less laborious by the availability on a commercial basis of suitable apparatus like (a) the sedimentation balance, (b) the automatic and semi-automatic equipments for counting and sizing from glass slides, microphotographs, and suspensions of powdered material, and (c) the electroformed precision microsieves for the determination of particle size distribution. The authors, apart from providing practical information and references of value on these apparatuses, have given the results of critical studies (by them as well as by others) of the application of the different apparatuses to size distribution measurement of the same powders (Chapter 9).

The treatment of size measurement by other methods like permeability, adsorption and light scattering by the authors is good, in spite of its being brief. However, sufficient references to literature are available at the end of Chapter 8 so that interested readers can study the subjects further.

The practical needs of those wanting to choose rapidly the appropriate method of size measurement for the sample in hand have been kept in mind by the authors in the guide procedures they have drawn up in Chapter 10.

The applications of particle size distribution measurements have been well dealt with in the first chapter. The importance of flow conditioning and cake inhibition agents to help in the techniques for the development of desired characteristics of powdered material is well discussed. These techniques, if suitably modified and adopted, may prove to be of benefit to the solution of dust problems in industry and mining.

The chapters on definitions, data presentation and mathematical treatment of particle size distribution data are well written, and would prove useful to those wishing to delve further into the subject.

The publication of this elegant book is timely, and is of value in the further development of the subject of particle size measurement. The book is warmly recommended for laboratories carrying out programmes of industrial research.

S. GURUSWAMY

ANALYTICAL CHEMISTRY OF THE ACTINIDE ELEMENTS by Alfred J. Moses (Pergamon Press Ltd, Oxford), 1963. Pp. 137. Price 45*s*.

This monograph contains all the important modern analytical methods for the actinides and has filled a need that has been felt by teachers and research workers in advanced analytical chemistry. Rapid growth in research on transuranium elements during the last decade brought forth the necessity to devise analytical methods for their separation, identification and quantitative estimation. Since the elements are essentially radioactive, classical methods of analysis have to be supplanted with the use of nuclear techniques. The necessity to provide sufficient information to the analyst to meet this special situation is at once recognized and the present monograph fulfils these requirements admirably.

The first three chapters include the introduction, nuclear properties and synthesis of the actinides and a brief but instructive information on nuclear instrumentation. This is followed by details about the treatment of samples which include two informative tables on the choice of solvents for the dissolution of ores, minerals and alloys containing actinide elements.

The methods of separation given in Chapter V include those based on oxidation-reduction and the differences in the extraction coefficients of the elements. Separations by precipitation, electrolysis, volatilization and solvent extraction by TTA and mesityl oxide have been summarized. Ion-exchange methods have justifiably received a more thorough treatment because of the fact that the isolation of elements 93-102 would be almost impossible without this technique. Some interesting results of these studies have been diagrammatically shown on pages 30-33. One cannot, however, fail to notice that classical chromatographic procedures including paper chromatography have received scant attention. Chapters VI-IX are devoted to modern instrumental methods of analysis and include radiometric, spectrophotometric, electrochemical, X-ray and fluorimetric procedures. Few experimental details have, however, been given. The non-instrumental methods are purely of the conventional type and include even the redox and complexometric titrations carried out potentiometrically or photometrically. By far the most interesting and instructive chapter of this monograph is the one dealing with isotopic analysis of uranium and a few other actinides. This technique has been described at length especially for the analysis of uranium and contains a wealth of coherent data packed in a few pages. A brief reference is made in the last chapter to high frequency titrations and photosensitized reactions.

The utility of the monograph has been enhanced by the nuclear data summarized in Appendix A-E and by the list of general references in Appendix G. Although, because of lack of space, only a few experimental details have been given, each chapter is followed by a list of original references which should enable the interested reader to get the necessary information. The monograph may, therefore, be used as an excellent reference book by research workers and ranks among the best available in the field.

G. S. DESHMUKH

LECTURES ON GAS CHROMATOGRAPHY — 1962, edited by Herman A. Szymanski (Plenum Press Inc., New York), 1963. Pp. 282. Price $ 10.00

This book is a collection of lectures presented at the Fourth Annual Gas Chromatography Institute held at Canisius College, Buffalo, New York, during April 1962. It consists of 13 chapters and a section on panel discussion. The first chapter deals with the theory of gas chromatography. There is a chapter on columns and column supports, two chapters on detectors, three on temperature programming and one on special techniques.

The book is addressed both to the beginner as well as to the specialist. The aim of the book, as set forth in the blurb of the dust cover, is to present a comprehensive survey of gas chromatography ' technology '. The book deals with the theory and practice of gas chromatography, and highly specialized aspects of design and performance characteristics of chromatographic units. The treatment of theory and practice of gas chromatography is inadequate and is based on other standard works. The specialized techniques described are based on the experience of the authors and are therefore useful.

The book is well printed and is recommended to the specialist in gas chromatography interested in the design and construction of chromatographic equipment.

M. V. BHATT

INORGANIC SYNTHESES: Vol. VII, edited by Jacob Kleinberg (McGraw-Hill Book Co. Inc., New York), 1963. Pp. xi+335. Price $ 8.95

The volume under review is the seventh in the series published by a board of editors, constituted of a group of distinguished inorganic chemists. It has maintained the pattern and the arrangement of the preceding volumes in the series, and describes with all essential details and technique carefully checked and tested methods for the preparation of a number of sixty-five inorganic compounds, arranged under eight different chapters following the order of Mendeleef's Periodic Classification of Elements into groups and sub-groups. In many cases, a critical survey of all the known methods has been prefixed as an introduction to the synthesis of the compound under view. Like the earlier volumes of the series, the present one is also characterized by the clarity and the workability of the procedures and techniques described. Any obscurity or lack of sufficient detail in the original publications has been eliminated. A considerable improvement of older procedures has also been made in many cases.

The preparations of a number of compounds of current importance and interest in the field of research in coordination chemistry have been described in the present volume. These include: carbonyl, cyclopentadienyl, cyclopentadienylcarbonyl and cyclopentadienylcarbonylhydride complexes of some transition metals as well as iron-labelled cyclopentadienyl iron complexes. Among other preparations particular mention may be made of hydrides of germanium, tin, arsenic and antimony, chlorine-labelled deuterium chloride, hexachlorodisiloxane, sulphur tetrafluoride, peroxydisulphuryl difluoride, etc.

The book is complete with original references and is provided at the end with index to contributors, subject index and formula index. The printing, paper and get-up leave nothing to be desired.

The volume will undoubtedly make a valuable addition to all libraries attached to institutions concerned with training and research in chemistry of an advanced type. The reviewer can wholeheartedly recommend it in particular to the students of inorganic chemistry.

P. RAY

ENRICHED URANIUM PROCESSING by Finis S. Patton, John M. Googin & William L. Griffith (Pergamon Press Ltd, Oxford), 1963. Pp. viii+282. Price 70s.

The subject dealt with in this book is of a highly specialized nature and is concerned with various aspects of handling and fabricating enriched uranium materials. A good deal of information with vast coverage of literature has been very well compiled including elaborate illustrations.

In the first chapter, the importance of enriched uranium processing, substantiated by facts and figures, has been stressed and the progress made along with the details of existing facilities in the various factories has been well presented. The process chemical operations have been discussed in good detail in the second chapter. However, the demarcation between low and high enrichment processing is not sufficiently emphasized. In the third chapter, various operations involved in the fabrication of metallic and ceramic fuel materials have been well presented. Though the various methods adopted for the manufacture of fuel for a good many of the existing reactors have been dealt with, mention has not been made of the specialized method of injection casting applicable to precision casting of small diameter fuel pins or rods. The health hazards and criticality considerations associated with the handling of enriched materials have been described in the fourth chapter under 'Radiation safety'. These will form a very good guide in planning the facilities for the manufacture of this type of fuel elements. With the increasing stress on international control of fissile materials, the fifth chapter dealing with uranium control is of special interest. The methods of analysis described for determination of uranium along with the procedures for estimating the isotopic contents will be very useful as a guide. The authors have included in the sixth chapter the various considerations involved in designing enriched fuel fabrication plants. The last chapter on the economics and management gives a general survey of cost factors involved in the fabrication of fuel for the American reactors. This can serve as a guide for adopting the procedures for collecting similar data in other countries.

The authors have achieved to a great extent the objective set forth for the preparation of the monograph, viz. to serve as a useful guide and as a reference book. Even though there are stray references to the work in USSR, the coverage is not adequate, specially in view of the progress made by that country in this field. The book can be highly recommended to scientists and engineers connected with nuclear power programmes and should be of special interest to chemical and metallurgical engineers connected with the production of fuel elements.

N. K. RAO

A HANDBOOK OF THE METALLURGY OF TIN by D. V. Belyayev; translated from the Russian by J. J. Carnish; English translation edited by H. T. Protheroe (Pergamon Press Ltd, Oxford), 1963. Pp. viii+122. Price 42*s*.

The book under review is an English translation by J. J. Cornish of the Russian edition by D. V. Belyayev published in Moscow in 1960, and presents in a basic and comprehensive way the theory and practice of the metallurgy of tin and its alloys both within and outside the iron curtain. The book, mainly intended for tin metallurgy operatives, more than meets the requirements.

The subject is covered in eleven chapters and the author, after a brief general survey on the art and science of tin metallurgy, proceeds to discuss in some detail the raw materials of the tin industry and the processes for preparing tin-bearing concentrates like roasting, magnetic separation and leaching. Smelting and reduction of tin concentrates in reverberatory and electric furnaces to obtain quality tin are detailed next. Separate chapters are devoted to the smelting of slags for the recovery of tin in a shaft furnace and smelting of secondary tin materials. A separate chapter is devoted to the production of quality tin and very pure tin by well-known methods like fire refining, electrolytic refining and zone melting. Details of dust collection and accident prevention have also been discussed and highlighted.

This 122-page book though concise presents a panoramic view of tin metallurgy and could be considered a very useful reference book for both students of metallurgy and operatives.

A. A. KRISHNAN

ELECTROMETALLURGY OF STEEL AND FERRO-ALLOYS by F. P. Edneral; translated from the Russian by P. Hardbottle (Current Book House, Bombay), 1962. Pp. xiii+576. Price Rs 35.00

The book under review which is the second edition of an English translation of the original Russian work by Edneral is the text of a course prescribed by the Ministry of Higher Education for the metallurgical colleges and institutes. The fast realization in most of the industrial countries to avail the cheaply available electrical power in preference to conventional fuels, either through necessity or design for the large-scale production of steels and ferro-alloys, has given the subject of electrometallurgy a distinct and important stature of its own. This book is the logical outcome of such an appreciation.

The subject matter in the book has been conveniently divided into two parts under seven separate sections. Under the caption 'arc furnaces for steel making' are included the most up-to-date data on electric furnaces regarding design and refractories, specially designs for top-charging furnaces, as also the related electrical equipments of significance to the modern output conscious metallurgical engineer. Discussing next the electric melting of steel in arc furnaces, the role and use of oxygen in the various stages of melting in the basic and acid processes and specifically in the process for manufacturing stainless steel from scrap using oxygen are described. The significance of the combined methods, duplexing and triplexing is also highlighted. The chapter on casting high quality steels describes very lucidly the process and quality control both in the furnace and the pitside, and in some detail the methods of combating non-metallic inclusions and methods of cleaning ingots.

In the second part of the book which deals mainly with the manufacture of ferro-alloys, the author describes in detail the typical furnace constructions, electrical equipments and continuous self-baking electrodes and follows this on with manufacturing techniques for the production of ferrosilicon, ferrochromium, ferromanganese, ferrovanadium, and lists some do's and don't's concerning accident prevention. The manufacture of ferrotitanium and ferromolybdenum is described in the last section.

In general, the book will be useful to students of electrometallurgy and also to metals engineers and

technologists interested in the practice of the production and use of 'electro-metals' and 'alloys', especially in the Soviet Union.

A. A. KRISHNAN

BRITISH TRANSISTOR, DIODE AND SEMICONDUCTOR DEVICES DATA ANNUAL 1963-64 edited by G. W. A. Dummer & J. Mackenzie Robertson (Pergamon Press Ltd, Oxford), 1963. Pp. lxxi+1610. Price £ 10

British transistor, diode and semiconductor devices data annual 1963-64 is the second in the series dealing with British transistor, diode and semiconductor devices manufactured and available in UK. The book is intended to be a reference book for the users of semiconductor devices.

The volume is divided into 10 main sections. The first two sections contain the addresses of 'Contributing manufacturers' and 'UK agents and subsidiaries of overseas manufacturers'. The next two sections are devoted to the 'Contents guide' for manufacturers and for device applications — presented nicely in an alphabetical order. Then there is a section on 'Concise details index' which indexes the contents in the name of the manufacturers, their products (types, etc.) with short description and main applications.

An interesting write-up appears in the next two sections on 'Construction and properties of typical diodes, transistors and semiconductor devices' and 'Operating principles, design and applications information — Transistors, diodes and semiconductor devices'. The former is an up-to-date short review on semiconductor devices. Here emphasis is on the underlying principle of manufacture of devices and its limitations in terms of frequency, power, etc. Pictorial and schematic representations of this material on various devices make it very good reading. The other section on 'Operating principles, design and application' on various devices also brings out very useful information such as use of heat sinks with silicon power transistors and transient ratings of power transistors, etc.

The last three sections of the annual are 'Transistor data sheets', 'Diode data sheets', and 'Semiconductor devices data sheets'. This portion comprises about 90 per cent of the volume. The data given are systematic and sufficiently detailed for the users and designers of electronic equipment.

The editors have achieved their objective in compiling, in a systematic manner, the detailed data on all the available semiconductor devices from British manufacturers under one cover. The editors, contributors and the publishers deserve all praise for bringing out this excellent data book on transistor family of devices. The printing and binding of the volume are of a high quality.

AMARJIT SINGH

LIVING EMBRYOS: An Introduction to the Study of Animal Development, by Jack Cohen (Pergamon Press Ltd, Oxford, and Macmillan Co., New York), 1963. Pp. ix+116. Price 12*s.* 6*d.*

The format of the book is derived from a teaching course given by the author in the Department of Zoology and Comparative Physiology, University of Birmingham. In most of the undergraduate classes in our country, the study of embryology is generally subordinated to anatomy, taxonomy and physiology. It takes the form of a purely descriptive science which evokes very little interest. The types chosen in the book, the lucid coverage and simple, yet clear, illustrations offer good examples for a clear understanding of such basic phenomena like cleavage, determination, fate maps, cell lineage, organizers, differentiation and organogenesis. The small size of the book limits coverage and, therefore, the book suffers from the obvious omission of detail in some cases which would otherwise be dealt with in a larger book. The appendix gives useful practical hints for the study of embryological material. This book should be of invaluable help in reshaping embryological teaching in many undergraduate classes in our country.

M. R. N. PRASAD

PLANKTON AND PRODUCTIVITY IN THE OCEANS by John E. G. Raymont (Pergamon Press Ltd, Oxford), 1963. Pp. viii+660. Price £ 5 10*s.*

Johnstone's *The marine plankton* (University Press of Liverpool, Hodder & Stoughton, London), which appeared in 1924, has been the only introduction and guide for beginners in plankton studies. Since then, the necessity for a suitable book on plankton incorporating all the researches during the last three decades has been felt. This is not to say that there have been no valuable publications; they have all been either popular accounts or too advanced, some on certain aspects only such as natural history and others reviews on particular topics scattered over several journals, but none of them presents an integrated account to fulfil a much desired role. The book under review meets the need for a good textbook for undergraduates in marine biology and as a grounding for research workers.

There are 18 chapters, a list of references and an index. Chapters I-IV deal with the aquatic environment and its physical properties — temperature, dissolved gases, salinity and currents. In Chapters V-X are treated the nature of the vegetation, planktonic as well as benthic, primary organic production by the plant elements, the factors affecting productivity — nutrients, light, temperature, organic micronutrients, inhibitors and grazing, by the animals, of the plant crop produced. Chapter XI gives a broad review of the seasonal succession of phytoplankters. The zooplankton, the next link in the food chain, its nature, distribution, migration, biology, etc., form the topics for Chapters XII-XV and XVII. The food cycles, bottom fauna and nekton are described in Chapter XVIII and in Chapter XVI a concise treatment is accorded to the bacteria and regeneration processes in the sea.

Thus, the author has brought in and dealt with in a balanced manner all aspects of marine planktonic studies, practically the cycle of life in the sea — production, consumption and regeneration — incorporating most of the recent work, particularly those investigations carried out with modern techniques. Naturally, the author has drawn upon investigations carried out in the temperate and arctic regions where,

of course, more work has been done. Nevertheless, one wishes that more space had been devoted to work done in the tropics as well — mostly since the last war — more so as our knowledge of marine life and production of matter in the tropics has been rather meagre until then. It is hoped that this lacuna will be filled up in the next edition, for such a valuable book is sure to run into more editions.

The book is admirably written, the style makes for easy reading and the large number of illustrations, tables and graphs help one to understand the theme well. The printing and the get-up are very good. The author and publishers deserve the gratitude of all planktologists for having brought out such a useful book. The cost may be beyond the reach of many students.

R. SUBRAHMANYAN

TEA MANUFACTURE by C. R. Harler (Oxford University Press, London), 1963. Pp. viii+126. Price 16*s*.

Rapid changes are taking place in the methods of tea manufacture in North East India, particularly as a result of the introduction of new types of machines, which achieve a more drastic and quicker distortion of the leaf than a conventional roller. Unfortunately, with the single exception of an excellent monograph by E. L. Keegel dealing exclusively with tea manufacture in Ceylon, no other comprehensive work on tea manufacture is available on the market. Dr Harler's book is, therefore, very timely. In the author's own words " the aim of the book is to outline the conditions of manufacture under which best possible black tea can be produced from the leaf brought to the factory, whatever the style of procedure ". The scope of the book can best be indicated by listing the 11 chapter headings, ' The preparation and manufacture of tea ', ' Relationship between fresh leaf and made tea ', ' The withering of tea leaf ', ' The rolling process ', ' The fermentation process ', ' The firing or drying of tea ', ' The classification, grading and sorting of tea ', ' The modern tea factory ', ' Factory management ', ' Tea tasting ' and ' The chemistry of black tea manufacture and the pharmacology of tea '.

The basic principles of tea manufacture have been adequately dealt with in the book; but, perhaps, because of its small size many points of detail are missing. This is indeed a pity because the book contains a volume of useful data generally in the form of tables, and the inclusion of further details of practical value would have considerably enhanced its value as a guide on tea manufacture meant to assist the planters.

In a book on tea manufacture, one would expect a few more details on the LDS system than an incomplete account of the process covered in less than half a page.

There are some mistakes and misleading statements, a few of which are given here:

On page 24 under ' Chemical changes during withering ', it is implied that during withering there is an increase in the concentration of proteins. The fact is that protein breakdown constitutes one of the most important chemical aspects of withering leading to an increase in amino acids at the expense of proteins. On the same page dealing with ' Losses of carbohydrates due to respiration during withering ', the term transpiration is used when respiration is meant. Again on the same page, considerable confusion is created when the word fermentation is mentioned when withering is intended. On page 112 it is stated that with orthodox manufacture as much as one-quarter of the oxidizable catechins may remain unchanged. Extensive data on individual polyphenolic contents of tea leaf and made tea indicate that only under-fermented teas will contain such a high proportion of unoxidized polyphenolic matter. On page 113 it is stated that the thearubigins result from the dimerization of theaflavins. The oxidation of the theaflavins to thearubigins is, at present, supposed to result from the opening up of the pyrogallol ring associated with the benzotropolone residue and not by dimerization as stated in the book.

An experienced planter seeking cut and dry answers to specific problems may find the book to be, somewhat, of limited value; but it can be warmly recommended as an introductory text to new factory assistants who wish to have broad grasp of the subject before they are actually called upon to grapple with the day-to-day realities of tea making.

The glossary of technical terms at the end of the book, the easy style of the author and the moderate price of the book are commendatory factors in its favour for use by the layman.

I. S. BHATIA

ELEMENTS OF ENGINEERING REPORTS by Dale S. Davis (Chemical Publishing Co. Inc., New York), 1963. Pp. 200. Price $ 8.50

Little attention seems to have been paid to the essentials of technical writing, especially at the graduate and postgraduate levels, with the result that technical papers from higher technical institutions, including laboratories and industries, call for extensive editing and sometimes partial recasting. Proper organization of the contents and effective presentation of ideas and data can be achieved only by cautious effort, keeping in view the four elements of good writing: accuracy, clarity, simplicity and readability. A number of books on technical writing have appeared and it is time to think of integrating a course of technical writing with curricula in science and engineering in the country. The need for improvement in the standard of presentation of technical information and more attention to the study of the language and literature as part of general science education has been felt even in England. The present book meets all essentials of a text-book for such a purpose.

It is interesting, in this connection, to recall the words of the author — a teacher with considerable practical experience: " Not long ago, a disgruntled student stepped into the office to complain about a report heavily marked in blue pencil. ' Why do you make so much fuss about correct English ? ' he asked. ' I ain't gonna be an English engineer. I'm gonna be an industrial engineer.' We agree on his first statement: definitely he is not going to be an English engineer, whatever that is. I have a good

idea that he is not going to be very successful industrial engineer, either — at least not until he is willing to take the time to improve his technical writing." It is needless to emphasize that knowledge is built from the written word and a well-organized and concise presentation is essential for easy reading, evaluation and utilization of the information. It is estimated that many engineers give 75 per cent of their time not to doing technical work itself but in communicating ideas about that work to other people (or the users of the information) and hence the ability to express correctly, clearly, concisely and effectively is a decisive factor in the career of the professional technologist or scientist.

The present book provides a comprehensive treatment of the elements of report writing and includes a number of illustrations and exercises. Common faults and various aspects of technical editing are also discussed.

The book traces the history of report writing from engineering reports in the Bible, e.g. that of Noah & Sons Inc. on their first and only venture of the Ark, the Greek, Egyptian and Roman military and engineering reports of the early centuries and the scientific reports of Harvey, Newton, Davy, Darwin and Hertz to Einstein which " have etched deep marks on the world of science and technology ".

The book has been planned to assist engineering students in preparing technical papers, reports and theses and to aid the instructors in editing and evaluating such written work. The book is also designed to guide practising engineers in writing reports and reviews and also to aid technical writers and editors in maintaining high standards of communication. The book deals thoroughly with the various elements of orderly presentation, such as appropriate composition and layout of titles (often neglected by authors and sometimes by the press), title page, table of contents, list of tables, list of figures, abstract (few comprehend the essentials and significance of abstracts), introduction (the essentials of which are often neglected), the body — comprising description of equipment, materials, procedure, results, discussion, conclusion and recommendations — and summary. The author recommends the direct form of expression, at least for analytical procedures, against the passive voice with the third person, which is ' usually clumsy and roundabout '. However, this has to be considered at one's own discretion.

Methods of bibliographic citations, presentation of appendices, tables and illustrations and graphical representation of engineering equations have been lucidly given. The common faults in writing, recommended practice, illustrative reports and corrections, the role of the technical editor, etc., are interesting and informative. Appendices relating to symbols, abbreviations and numerals, precision of measurements, spelling and proof-reading, etc., are included.

This book, along with the numerous other books on technical writing, should be read by all scientists and engineers desirous of effective and easy communication. It will also serve as a useful guide to technical editors.

K. RAJAGOPALAN

A SYMPOSIUM ON TEACHING RUSSIAN edited by C. V. James (Pergamon Press Ltd, Oxford), 1963. Pp. xi+143. Price 21*s*.

THE PSYCHOLOGY OF TEACHING FOREIGN LANGUAGES by B. V. Belyayev; translated from the Russian by R. F. Hingley (Pergamon Press Ltd, Oxford), 1963. Pp. ix+230. Price 30*s*.

RUSSIAN ORTHOGRAPHY edited by L. A. Cheshko; translated from the Russian by T. J. Binyon; English translation edited by C. V. James (Pergamon Press Ltd, Oxford), 1963. Pp. xv+147. Price 15*s*.

RUSSIAN PUNCTUATION edited by L. A. Cheshko; translated from the Russian by T. J. Binyon; English translation edited by C. V. James (Pergamon Press Ltd, Oxford), 1963. Pp. viii+54. Price 7*s*. 6*d*.

MODERN RUSSIAN USAGE by D. E. Rozental; translated from the Russian by M. A. Green; English translation edited by C. V. James (Pergamon Press Ltd, Oxford), 1963. Pp. x+131. Price 16*s*. 6*d*.

The importance of Russian in the present-day world cannot be overexaggerated and nobody today can deny the need for more serious study of the language. After the launching of sputniks by the Soviet Union the importance of learning Russian is being more and more realized throughout the world, and an increasing number of institutions are offering courses in Russian language.

On teaching Russian deals with the problems and methods of teaching Russian. The article on ' The role of the mother tongue in the teaching of modern languages ' is quite interesting. The author rightly points out that certain absolute minimum use of the mother tongue is necessary in the elementary stage and warns that too much time should not be wasted on " stating things about the language ".

The article on ' Audio-visual methods of language learning ' gives a lucid picture about the working of the methods in practice. There is, no doubt, that language teachers should make maximum use of the tape recorder and the film strip projector, the two modern aids for learning to speak and read the language. Indian teachers should not fall behind in utilizing and developing these and new techniques.

The psychology of teaching foreign languages is an excellent translation by Dr R. F. Hingley of the original Russian book of B. V. Belyayev, Professor of Methodology, Moscow State University. Prof. Belyayev has based his work on a study of Soviet schools. According to him the psychology of teaching foreign languages should play a very important role in the teaching of foreign languages in schools and the data furnished by psychology should serve as the basis. So the teachers of foreign languages should be familiar with the laws and principles of this psychology. The discussion on some basic problems in the psychology of language which we find in this book will go a long way to convince the teacher that language teaching requires a most thoughtful attitude. Thinking in a foreign language and proper feeling for

that language should undoubtedly be the basic objectives. Our teachers should make a good use of this valuable book.

The Russian book *Pravila Russkoi orfografii* has been translated and published in two separate volumes, *Russian orthography* and *Russian punctuation*. There was a necessity for codification and improvement of modern Russian orthography even after its reform and simplification in 1918. A number of variations and contradictions accumulated in Russian orthography and up to 1956 no complete authoritative collection of the rules of Russian orthography existed. After the publication of this book containing codification and regularization of modern spelling, its contents were confirmed by the Academy of Sciences of the USSR and the Ministry of Higher Education of the USSR. Quite a number of distinguished Soviet philologists including academicians and corresponding members of the Academy of Sciences of the USSR took part in the compilation of this collection. "They (the present rules) are indispensable as a practical aid for all those interested in questions of Russian orthography." This book is a must both for teachers and students of Russian. There is a complete vocabulary and index given at the end.

Students are usually under the wrong impression that Russian punctuation is more or less the same as English punctuation. Russian punctuation which is generally not found in text-books and grammar needs careful study and students should pay more attention to the use of comma and dash in Russian. The book gives in detail, and with useful examples, the rules of punctuation.

Modern Russian usage is an adaptation and translation of D. E. Rozental's *Kultura rechi*, published by the University of Moscow in 1959. There was rapid development of the Russian language over the past forty-five years keeping pace with the developments in the Soviet Union in various fields of culture and economy. Consequently, the need was felt for normalization of the literary language in the fields of lexicology, grammar, pronunciation, terminology, etc. Rozental's book serves this purpose to a very great extent. The teacher and student of modern Russian will find in this book the answers to many intriguing and difficult questions which are usually not available in other works of reference. The book is of immense value for the foreigners and every Indian teacher of Russian should have a copy of this book for ready reference.

These translations published by the Pergamon Press are rather expensive, though the quality of printing and paper is very good.

C. N. CHAKRAVARTI

PUBLICATIONS RECEIVED

PROCEEDINGS OF THE REGIONAL SYMPOSIUM ON DAMS AND RESERVOIRS, TOKYO, JAPAN, 18-23 SEPTEMBER 1961 (Flood Control Series No. 21) (United Nations, New York), 1962. Pp. viii+238. Price $ 3.00

FIELD METHODS AND EQUIPMENT USED IN HYDROLOGY AND HYDROMETEOROLOGY (United Nations, New York), 1962. Pp. ix+127. Price $ 1.50

REVIEWS IN FOOD SCIENCE AND TECHNOLOGY: Vol. 4, 1962 (Association of Food Technologists, Central Food Technological Research Institute, Mysore), 1963. Pp. xvi+255. Price Rs 8 or 15*s*. or $ 2.00

SYMPOSIUM ON ADVANCES IN TECHNIQUES IN ELECTRON METALLOGRAPHY, NEW YORK, NY, 26 JUNE 1962 (American Society for Testing & Materials, Philadelphia), 1963. Pp. v+72. Price $ 3.25

CONSTITUTIONAL PROBLEMS IN ORGANIC CHEMISTRY by M. B. Watson & G. W. Youngson (D. Van Nostrand Co. Ltd, London), 1963. Pp. 136. Price cloth bound, 30*s*.; paper bound, 18*s*.

RADIATION AND OPTICS: AN INTRODUCTION TO THE CLASSICAL THEORY by John M. Stone (McGraw-Hill Book Co. Inc., New York), 1963. Pp. xvi+544. Price $ 11.75

THE CHEMICAL INDUSTRY: VIEWPOINTS AND PERSPECTIVES edited by Conrad Berenson (Interscience Publishers, a Division of John Wiley & Sons Inc., New York), 1963. Pp. x+426. Price $ 10.00

DICTIONARY OF ARCHITECTURE AND BUILDING TRADES (in Four Languages: English, German, Polish & Russian) edited by A. Zboinski & L. Tyszynski (Pergamon Press Ltd, Oxford), 1963. Pp. 491. Price £ 7

HIGH POLYMERS: Vol. XIII — POLYETHERS, Part I — POLYALKYLENE OXIDES AND OTHER POLYETHERS edited by Norman G. Gaylord (Pergamon Press Ltd, Oxford), 1963. Pp. xiv+491. Price $ 16.00

SCIENCE AND TECHNOLOGY FOR DEVELOPMENT: Vol. 1 — WORLD OF OPPORTUNITY (Report on the United Nations Conference on the Application of Science & Technology for the Benefit of the Less Developed Areas) (United Nations, New York), 1963. Pp. viii+267. Price $ 6.00

MODERN APPLICATIONS OF PHYSICAL OPTICS by M. Francon; translated from the French by Scripta Technica (Interscience Publishers, a Division of John Wiley & Sons Inc., New York), 1963. Pp. viii+106. Price $ 4.50

CONCEPTS IN PHOTOCONDUCTIVITY AND ALLIED PROBLEMS by Albert Rose (Interscience Publishers, a Division of John Wiley & Sons Inc., New York), 1963. Pp. x+168. Price $ 5.95

QUANTUM THEORY OF SOLIDS by C. Kittel (John Wiley & Sons Inc., New York), 1963. Pp. xi+435. Price $ 13.50

THE ADIABATIC MOTION OF CHARGED PARTICLES by Theodore G. Northrop (Interscience Publishers, a Division of John Wiley & Sons Inc., New York), 1963. Pp. xiv+109. Price $ 5.95

AUTOMATIC CONTROL AND COMPUTER ENGINEERING: Vol. 2, edited by V. V. Solodovnikov; English translation edited by Tribhuvan Prasad (Pergamon Press Ltd, Oxford), 1963. Pp. vii+331. Price £ 5 net

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John Wiley & Sons Inc., New York), 1963. Pp. vii+585. Price $ 12.00

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GRAVIMETRIC ANALYSIS: Vol. 1, by Laszlo Erdey; translated by Gyula Svehla (Pergamon Press Ltd, Oxford), 1963. Pp. viii+324. Price 50*s*. net

SYMMETRY — AN INTRODUCTION TO GROUP THEORY AND ITS APPLICATIONS by R. McWeeny; edited by E. A. Guggenheim, J. E. Mayer & F. C. Tompkins (Pergamon Press Ltd, Oxford), 1963. Pp. xiv+248. Price 50*s*. net

GENETICS TODAY: Vol. 1 — ABSTRACTS edited by S. J. Geerts (Pergamon Press Ltd, Oxford), 1963. Pp. 332. Price 100*s*.

THE ELECTRONIC THEORY OF CATALYSIS IN SEMICONDUCTORS by F. F. Volkenshtein; translated by N. G. Anderson (Pergamon Press Ltd, Oxford), 1963. Pp. vi+169. Price 50*s*. net

ORGANIC GEOCHEMISTRY — International Series of Monographs on Earth Sciences: Vol. 16, edited by Irving A. Breger (Pergamon Press Ltd, Oxford), 1963. Pp. x+658. Price £ 7 net

STELLAR INTERIORS by Donold H. Menzel, P. L. Bhatnagar & Hari K. Sen (Chapman & Hall Ltd, London), 1963. Pp. xiii+347. Price 65*s*.

ADVANCES IN MACHINE TOOL DESIGN AND RESEARCH edited by S. A. Tobias & F. Koenigs-Berger (Pergamon Press Ltd, Oxford), 1963. Pp. 497. Price £ 8 net

FIFTY YEARS OF SCIENCE IN INDIA — PROGRESS OF MEDICAL SCIENCE by V. R. Khanolkar (Indian Science Congress Association, Calcutta), 1963. Pp. 50. Price Rs 1.50

FIFTY YEARS OF SCIENCE IN INDIA — PROGRESS OF GEOLOGY by S. Ray (Indian Science Congress Association, Calcutta), 1963. Pp. 194. Price Rs 3.75

THERMODYNAMIC ASSESSMENT OF ROCKET ENGINES by B. A. Nikolayev; translated from the Russian by W. E. Jones (Pergamon Press Ltd, Oxford), 1963. Pp. xii+150. Price 63*s*. net

EXTRACTION AND METALLURGY OF URANIUM, THORIUM AND BERYLLIUM by R. G. Bellamy & N. A. Hill (Pergamon Press Ltd, Oxford), 1963. Pp. ix+198. Price 42*s*. net

SHORTER TECHNOLOGICAL DICTIONARY (POLISH/ENGLISH, ENGLISH/POLISH) edited by S. Czerni & M. Skrzyka (Pergamon Press Ltd, Oxford), 1963. Pp. 244. Price 70*s*. net

ADAPTIVE CONTROL SYSTEMS edited by Felix Caruthers & Harold Levenstein (Pergamon Press Ltd, Oxford), 1963. Pp. viii+290. Price 80*s*.

THEORY OF AUTOMATIC CONTROL by M. A. Aizerman; translated from the Russian by Ruth Feinstein (Pergamon Press Ltd, Oxford), 1963. Pp. xi+519. Price £ 4 net

PHYSICS OF FAILURE IN ELECTRONICS by M. F. Goldberg & Joseph Vaccaro (Spartan Books Inc., Baltimore, and Cleaver-Hume Press Ltd, London), 1963. Pp. 255

OPTICAL ACTIVITY AND CHEMICAL CONSTITUTION by Bawa Kartar Singh & O. N. Perti (Asia Publishing House, Bombay), 1963. Pp. xii+149. Price Rs 8.00

MATHEMATICAL TECHNIQUES OF OPERATIONAL RESEARCH by L. S. Goddard (Pergamon Press Ltd, Oxford), 1963. Pp. x+230. Price 42*s*. net

NOTES & NEWS

A new antiparticle — Anti-xi zero

The anti-xi particle, the 32nd of the known fundamental particles and theoretically predicted earlier, has now been detected by a group of workers belonging to the Yale University and Brookhaven Laboratory. The anti-xi zero particle having no electrical charge and a mass 2590 times that of the electron was detected by the trace left in a bubble chamber by its decay products. The collisions between protons and antiprotons were observed in a bubble chamber and only three of the 300,000 photographs taken of the tracks in the bubble chamber gave evidence for the production of the new particle [*Discovery*, **24** (No. 10) (1963), 7].

Controlled thermonuclear power — A new approach

A new approach to the problem of producing controlled thermonuclear power has been suggested by E. R. Harrison of the Rutherford High Energy Laboratory, Berkshire, UK.

The basis of the proposed approach is as follows: Macroscopic particles (macrons) are accelerated to velocities of 10^8-10^9 cm./sec. and made to collide either with other particles or with a target. Their kinetic energy is thus converted into thermal energy which is initially confined to a small region for a short period of time. The theoretical analysis, based on the assumptions (i) that the energy radiated from the impact region is small compared with the initial kinetic energy and (ii) all reaction products escape from the impact region, shows that the ratio of energy released to the energy supplied can have a value greater than 1 under certain conditions. Though the analysis is based mainly on the assumption that the particles and the target consist solely of hydrogen isotopes, it can also be extended to other cases.

However, the practical feasibility of this new approach depends upon the development of new techniques for accelerating macrons to velocities of 10^8-10^9 cm./sec. [*Phys. Rev. Lett.*, **11** (1963), 535].

A new type of radioactivity

A new type of radioactivity — the emission of protons from the nucleus of nickel bombarded by Ne-20 ions — has been discovered by Victor Karnauknov and coworkers of the Joint Nuclear Research Institute at Dubna near Moscow. The same group of scientists had earlier predicted as a result of theoretical investigations the possibility of this type of radioactivity along with the most suitable reaction conditions for their production.

The energy of the emitted protons and the life of proton-active nuclei were determined by a special technique in which the newly born radioactive nuclei were carried by fast rotating discs to a decay monitor which 'sensed' the desired nuclei. A gas-filled counter was used to measure the deceleration rate of the nuclei during the emission of protons and a semiconductor counter was used to determine their total energy.

It has been found that the reaction produced two different sources of protons. One of these sources was formed by the transfer of nucleons from the neon to the nickel during the collision of their nuclei. The protons emitted in this process have an energy of 5 meV. and the nucleus has a half-life period less than $\frac{1}{10}$ sec. The other isotope was produced by a reaction in which the Ne-20 and nickel nuclei fused together to form finally a light isotope located between selenium and strontium in the periodic table. This isotope with a half-life of 25 sec. was found to emit protons of 2-3 MeV. energy. One of the mechanisms suggested for this phenomenon is as follows: The nuclear reaction produces a proton-overloaded nucleus which undergoes positron emission. The daughter nucleus is extremely unstable, as it is still overloaded by protons. Therefore, a slight additional excitation is enough to cause the emission of protons.

Another hypothesis envisaging a double-proton radioactivity, i.e. the emission of two protons by a single nucleus simultaneously, has also been put forward by Vitaly Goldansky of the Soviet Academy of Sciences to explain the mechanism of the observed radioactive emission [*Sov. Features*, **1** (No. 2) (1963), 2].

Stable variable magnetic fields

A method of achieving stable magnetic fields, the strength of which can readily be changed, has been developed at the Bell Telephone Laboratories, New York. Till now, stable magnetic fields were difficult to obtain as the slightest change in power supply to the electromagnet varies the field. In this method, a 15-mil thick superconducting tube (inner diam., $\frac{1}{2}$ in.) made of niobium-zirconium alloy is used to stabilize the magnetic field. A strong magnetic field is applied along the axis of the tube, thus inducing a current to flow in the tube. Once the current is started, it will persist as long as the tube is kept cooled to −269°C. The current creates a magnetic shield around the portion of the field that is inside the tube. Even if the applied field intensity changes by a few hundred gauss the field inside the tube will remain fairly constant. To obtain a higher intensity, the applied field is increased until the internal field reaches the desired strength; then the applied field is reduced slightly to the middle of the stable range. The superconducting tube stabilizes the field at the new intensity. For obtaining a lower field the procedure is reversed.

The method is expected to find application where stable and controllable magnetic fields are required in experiments at temperatures near absolute zero. It has already been used to investigate the nature of the transition state in superconductors [*Technical News Briefs from Bell Telephone Laboratories, New York*, **2** (No. 5), October 1963].

An instrument for determining atmospheric ozone

A new compact and inexpensive instrument for the evaluation of

the ozone content of the atmosphere has been designed and fabricated at the Cavendish Laboratory, University of Cambridge. The Dobson spectrophotometer which has been accepted internationally as the standard instrument for the evaluation of ozone in atmosphere lacks the facility for continuous observation and requires considerable skill in operation. The method of photographing the radiations from the stars necessitates an elaborate telescopic system.

In the new apparatus, two wave bands *A* and *B* in the ultraviolet region, of which *A* is more strongly absorbed by ozone than *B*, are isolated by a monochromator and their relative intensities are measured and the ozone content of the atmosphere is determined from the ratio of these intensities following the usual procedure. The radiations in the two wave bands are allowed to fall on separate photomultipliers and the measurement of intensities is made using the pulse counting technique. In the apparatus fabricated, an 8 in. telescope objective is used with a monochromator consisting of a reflexion grating. Suitable filters immediately in front of the photomultipliers effectively cut off stray light and hence the apparatus could be used even in a well-lit room. Accurate control of the wavelength setting is achieved by the use of a mercury lamp. Observations made of bright stars for several days during winter and spring of 1962-63 by choosing the *A* band to cover the range 3100-3150 A. and the *B* band the region 3220-3250 A. have given a value of the ozone content of (402±12) m. atm. cm.

By directing the instrument towards the clear zenith sky the second Umkehr observation in addition to the usual Umkehr observation is clearly seen [*Nature, Lond.*, **199** (1963), 1177].

Laser-cum-phonon oscillations

Scientists at the Bell Telephone Laboratories have recently reported a new phenomenon in which both laser and lattice oscillations (phonons) are excited in a crystal of magnesium fluoride doped with nickel ions. This material is unique in that it 'lases' at a wavelength that is determined partly by vibrations of the crystal lattice near the nickel ions and partly by electronic states of the nickel ions. In previous lasers, the wavelength of the emitted laser light is determined solely by electronic transitions.

In the new laser, nickel ions are excited to high states of energy by optical pumping in the usual way; then they relax back to the upper laser level. From this level, which is an electronic state of nickel in the magnesium fluoride lattice, the ions fall to the lower laser level, emitting the photon associated with laser action. At this lower level the nickel ions are in the ground state and, therefore, are unexcited. The laser oscillation does not occur in the purely electronic transitions of the nickel ions because the photons emitted at these shorter wavelengths tend to be absorbed in the crystal; on the other hand, the lattice is vibrationally excited. The longer wavelength photons associated with the phonon generation are not absorbed so much, and most of them are, therefore, available to stimulate further emission.

Thus part of the energy of excitation is converted to vibrational energy by the generation of a phonon in the crystal lattice. The frequency of the laser oscillation is partly determined by the energy of this phonon. The larger the phonon energy, the lower the laser frequency. Thus the laser oscillation results not from a nickel ion transition alone but from a transition of the crystal as a whole.

With the crystal at either 20° or 78°K., the wavelength of laser emission has been found to be at 1·62 μ, the phonon frequency associated with the photon emission being 10^{13} c/s. [*News from Bell Telephone Laboratories, New York*].

A new method for studying the olfaction of alcohols

A galvanic method reported for studying the olfaction of alcohols enables the detection of specific alcohol vapours with a sensitivity 100 times better than that possible with the human nose. The method can be used in such fields as antipollution enforcement, medical diagnosis, odour control, air conditioning and testing of alcohol intoxicants.

In the new method, a droplet is set up between two electrode. Then a vapour is flown on the droplet and the change in current is recorded as a function of time. The cell consists of a platinum gauze and a graphite electrode partially immersed in a closed beaker containing an electrolyte and a stirrer. Nitrochromic acid is used as the electrolyte. The changes in current are recorded by an electrometer-recorder arrangement.

Alcohols containing carbon atoms ranging from 4 to 10 have been studied. Filtered air is passed through a solution of the alcohol in mineral oil. Then the air containing the alcohol vapour is passed into the cell. This produces a rapid change in current. After some time, the current becomes constant. When filtered air is again passed into the solution another change is recorded in the reverse direction. Best results are obtained at a flow rate of 0·2-0·4 ml./sec. An alcohol solution of concentration $10^{-5}M$ or more can be detected with the cell system [*Chem. Engng News*, **41** (38) (1963), 51].

Krypton difluoride

Krypton difluoride has been obtained for the first time as a white crystalline solid, stable at −30°C., by irradiating krypton and fluorine at −150°C. with an electron beam. The reaction has been carried out in a cylindrical 3-litre nickel vessel, 15 cm. in diameter. The 1·5 MeV. electron beam is allowed to enter through a 0·013 cm. nickel window welded on the inner end of the re-entrant tube projecting 3·1 cm. into the vessel. Such an arrangement diminishes the radiation intensity at the front wall of the vessel, and should permit accumulation of products there which otherwise might decompose in the main part of the beam. The cooling to −150°C. was accomplished by means of two heavy copper straps wrapped around the vessel and soft soldered to it, their ends dipping into liquid nitrogen. The pressures of the reactants at room temperature were approximately 1 atm. each, with fluorine in slight excess.

After the irradiation, excess krypton and fluorine were pumped

away while the reaction vessel slowly warmed up. The vessel was then connected to a glass vacuum system containing a fused quartz U-tube and the product was frozen out in the U-tube while pumping continued. Small amount of KrF_2 began to come out while the vessel was at −60°C., but the bulk of it was obtained between −40° and −30°C. When trapped by dry ice or liquid nitrogen, the compound is obtained as a finely divided solid.

Volatility of the compound is apparently similar to that of KrF_4, since the vapour pressure measured at −40°C. (assuming no decomposition) is 1·5 mm. The composition of KrF_2 has been established by decomposing a sample with mercury and analysing the reaction products. It is assumed that KrF_2 is thermodynamically less stable than KrF_4 [*Science*, **141** (1963), 1171].

Microdetermination of sulphur in organic compounds

An improved method for the volumetric microdetermination of sulphur in organic compounds is described which involves fusion of the sample with sodium peroxide in a metal bomb, removal of sodium from the aqueous extract of the fusion product by means of a cation-exchange resin and titration of the sulphate ion with barium perchlorate.

In a dry nickel 'fluorine bomb' is placed powdered sodium peroxide (0·5 g.), a suitable weighed amount of the sample (5-15 mg.) and a further 0·5 g. of sodium peroxide. The contents are mixed well by rotation and the bomb is heated in a muffle furnace for 3 min. at 650°. The bomb is cooled and the fusion product extracted by placing the bomb in a small beaker containing 10-15 ml. of water and warming until effervescence ceases. After rinsing the bomb and the lid with water, the combined solution is quantitatively transferred to a 50 ml. calibrated flask and made up to the required volume by dilution.

For the removal of sodium from the fusion product extract, 30 g. of the cation-exchange resin, Amberlite IR-120(H) is placed in a conical flask. Ethanol (25 ml.) is then added and the flask is shaken well for about 1 min. after which ethanol is removed by decantation. This process is repeated with a further 20 ml. ethanol. Fusion product extract (25 mg.) is then added to the resin and the flask shaken again for 5 min. and the solution is decanted into a suitable conical titration flask containing a magnetic bar. The resin is rinsed with 4 successive 25 ml. portions of ethanol and the washings are mixed with the contents of the titration flask. Thorin and methylene blue indicator solutions (0·1 ml. each) are added and the contents of the titration flask titrated with 0·01*N* barium perchlorate to a pink end-point colour persisting for about 20 sec. End-points in the titration may give erroneous results if the ethanol washed resin is set aside for more than 2 hr. Analysis of several organic compounds, including some containing nitrogen, chlorine, fluorine as additional elements have been tried and the results obtained are quite accurate [*Analyst*, **88** (1963), 791].

Extraction of silicate structure from mineral silicates

A technique for extracting the silicate portions intact from mineral silicates has been developed at the Dow Corning Corporation, Midland, USA. The technique is based on the fact that some of the silicate minerals react with acids, releasing their silicate portions to the liquid portion as silicic acids. Silicic acids, though unstable, can be reacted with monofunctional organosilicon compounds to give stable organosilyl silicate derivatives of the acids. Thus, simultaneous acid leaching and trimethylsilyl end-blocking of silicate minerals give silicates having the same silicate structure as the mineral from which they are derived. Using the new technique, the silicate structures in orthosilicates, pyrosilicates and tectosilicates have been extracted and studied [*Chem. Engng News*, **41** (38) (1963), 44].

Carbon skeleton detection of organic compounds

Neutral palladium catalyst (1 per cent) has extended the useful range of a hydrogenolytic gas chromatographic technique for determining carbon skeleton and other structural features of the organic compounds. During the reaction, oxygen, nitrogen, sulphur and halogen atoms are stripped from the molecule and the multiple bonds are saturated giving rise to parent compounds or higher homologues. The reaction products, which are analysed on a flame ionization chromatograph, provide information on the carbon skeleton of the compounds, in addition to other structural features.

Any flame ionization gas chromatograph can be adapted to use the technique by inserting a special catalyst containing tube between the injection part and the chromatographic column. The carrier gas must be hydrogen and, therefore, it is not necessary to add hydrogen at the flame-detector head. Usually 10-20 μg. of the material are enough for a single analysis. The neutral catalyst is prepared by adding non-volatile base to neutralize the hydrochloric acid formed during catalyst activation process. The neutral catalyst allows analysis of amines and, in addition, has increased the range of the technique to include compounds with at least 20 carbon atoms. The catalyst is not poisoned by sulphides unlike platinum catalyst and causes much less ring cleavage than does platinum [*Chem. Engng News*, **41** (28) (1963), 54].

Intramolecular rearrangement of benzene rings in diphenyl

Unequivocal evidence has been obtained for the water promoted, aluminium chloride induced intramolecular rearrangement of the benzene rings in diphenyl. When diphenyl-1,1′-C^{14}, prepared via an Ulman reaction on iodobenzene-1-C^{14}, was heated to 100°C. for 30 min. with aluminium chloride (10 moles per cent) and water (1 mole per cent), the radioactivity originally localized at the two connecting carbons had been randomly distributed. Recovered active diphenyl has also been shown to be randomized when the reaction was carried out for 12 hr in refluxing benzene solution. The view that the reaction is intramolecular is supported by the facts that (i) the inactive benzene used in the solvent experiments was devoid of activity

and (ii) a rearrangement carried out with inactive diphenyl in benzene-1-C_1^{14} yielded diphenyl having an activity of less than 0·001 per cent intermolecularity. On the basis of the results obtained, it appears that the significance of isomer distribution in diphenyl would require re-examination [*J. Amer. chem. Soc.*, **85** (1963), 3308].

Peptide synthesis

The preparation of pure, radioactive prolylhydroxyproline or any other peptide that tends to cyclize has been made possible as a result of investigations carried out at the Institute of Muscle Diseases, New York City.

In the new synthesis, proline is reacted with carbobenzoxychloride to yield carbobenzoxyproline which is converted to the acid chloride by treatment with phosphorous pentachloride in ether. The acid chloride-ether solution is filtered in dry nitrogen atmosphere to avoid atmospheric oxygen and moisture. To this is then added hydroxyproline in the presence of 4*N* sodium hydroxide. The product obtained after working up is carbobenzoxyprolylhydroxyproline. The removal of carbobenzoxy group is achieved by adding dry acetic acid saturated with anhydrous hydrogen bromide at a rate of 5 g. solution/g. of carbobenzoxy compound. The reaction is mildly exothermic and carbon dioxide is evolved. Although carbon dioxide evolution ceases within 15 min., the reaction vessel is allowed to stand for an additional 45 min. to ensure the completion of the reaction. Then large amount of anhydrous ether is added to precipitate hydrobromide salt of the dipeptide as a viscious oil; refluxing the oil with several portions of ether furnishes a hygroscopic granular solid. The pure dipeptide is obtained by running the hydrogen bromide through a Dowex 1 ion-exchange column in the hydroxyl form. The compound is added in a small amount of water and eluted with 1*N* acetic acid [*Chem. Engng News*, **41** (28) (1963), 52].

New biogenetic-type alkaloid synthesis

Hydroxylated 1-benzy- and 1-alkyl-tetrahydroisoquinolines have been found to undergo oxidative condensation in a manner resembling that occurring in alkaloid biosynthesis if their nitrogen atom is protected by quaternization. This reaction has been applied successfully in case of quaternary derivatives of coclaurine and lophocerine which on oxidation with one equivalent of ferric chloride or potassium ferricyanide give dimeric condensation products with a diphenyl-ether linkage. This unusual formation of diphenyl ethers has been explained as due to the fact that the mesomer with the radical at C-8 produced on oxidation of the hydroxyl at C-7 is sterically hindered and condenses with a second isoquinoline residue only if the latter is kept at a distance by an oxygen atom between the residues [*Angew. Chem. internat. Edit.*, **2** (1963), 551].

Total synthesis of steroids

A commercially feasible total synthesis of steroids which can be extended to the preparation of a wide variety of 13-alkyl-gona-1,3,5(10)-triene derivatives has been developed at the Wyeth Laboratories, Philadelphia, USA. The synthesis also makes feasible a commercial total synthesis of estrone and related therapeutic agents.

The starting material for the synthesis is 6-methoxy-1-tetralone which is converted into the key intermediate 13-alkyl-gona-1,3,5-(10),8,14-pentaene by reaction with vinyl magnesium chloride and condensation of the resulting vinyl alcohol with 2-alkylcyclo-aklane-1,3-dione to give an 8,14-secogonatetraene and acid cyclodehydration.

The above intermediate through a series of steps including reaction with 2-ethylcyclopentane-1,3-dione is converted into (±)-13-ethyl-3-methoxygona-1,3,5(10),8,14-pentaen-17-one. This compound is hydrogenated to saturate the D ring, ethynylated at C-17 (alpha substitution) and hydrogenated again. The 17α-ethyl intermediate is further reduced stereo-specifically with lithium in aniline and ammonia. Ring A with the 3-methoxy group is then reduced by a Birch reduction. Subsequent acid hydrolysis gives the required anabolic agent. The sequence to the progestational agent is similar, except that the ethynyl group is retained at C-17α [*Chem. Engng News*, **41** (34) (1963), 32].

Mode of action of actinomycin D in protein synthesis

The brightly coloured, peptide antibiotic actinomycin D discovered by Leo C. Vinning and S. A. Waksman [*Science*, **120** (1954), 389] has assumed enormous importance in studies on nucleic acid and protein syntheses as well as viral replication. It is highly toxic to higher organisms and several gram-positive bacteria, and inhibits the growth of a number of natural and experimental tumours.

E. Reich, R. M. Franklin, A. J. Shatkin and E. L. Tatum [*Science*, **134** (1961), 556] were the first to report that in mammalian cells in culture actinomycin D causes a selective inhibition of cellular RNA synthesis leading to a fall in cellular protein synthesis. No change in glycolysis or respiration of actinomycin D inhibited cells, e.g. in *Staphylococcus aureus*, has been recorded and as such its interference in energy production is not a significant possibility. J. M. C. Kirk [*Biochem. biophys. Acta*, **42** (1960), 167] has reported a complex formation between DNA and actinomycin D resulting in a spectral change of the latter compound. At least 100 times more RNA than DNA has been reported to be required for complex formation with actinomycin D [Rauen, H. M., Kersten, H. & Kersten, W. Z., *Z. physiol. Chem.*, **321** (1960), 139].

Since DNA acts as a template for RNA synthesis, the complexing of DNA by actinomycin D provides a concrete physical basis for its inhibitory effect on RNA synthesis. The specificity of the action of the antibiotic is further established by the fact that at concentrations at which cellular RNA synthesis is profoundly inhibited, DNA synthesis is affected only to a limited extent. Studies with mammalian and bacterial extracts have revealed that the *in vivo* action of this inhibitor is to inhibit the RNA polymerase profoundly but it does not significantly affect the DNA

polymerase [Hurwitz, J., Furth, J. J., Malamy, M. & Alexander, M., *Proc. nat. Acad. Sci., Wash.*, **48** (1962), 1222]. Since actinomycin D forms a complex with DNA, the specific effect on RNA polymerase has been attributed to the enzymes catalysing DNA biosynthesis and DNA-dependent RNA biosynthesis having a probable significant difference in their stereochemical relationship to the DNA molecule [Reich, E., Franklin, R.M., Shatkin, A. J. & Tatum, E. L., *Proc. nat. Acad. Sci., Wash.*, **48** (1962), 1238]. In an attempt to correlate the antibiotic action on DNA-dependent RNA synthesis and its binding to DNA, E. Reich, I. M. Goldberg and M. Rabinowitz [*Nature, Lond.*, **196** (1962), 743] have found that several actinomycins like B-aminoethyl actinomycin D, which do bind to DNA as effectively as actinomycin D, do not inhibit RNA synthesis to a similar extent. No explanation for this observation has been possible except that the demonstration of some variations in binding might require ionic conditions other than those used in their experiments, or alternatively, differences in biological activity may reflect not merely the quantitative aspects of binding of actinomycins, but might also be partially determined by the structural features of the different bound forms or of the complex with DNA.

Eunice Kahan, F. M. Kahan and J. Hurwitz [*J. biol. Chem.*, **238** (1963), 2491] have proposed an explanation for the specific action of actinomycin D. It has been shown that at low concentrations of actinomycin, each dGMP residue of the primer DNA is potentially able to bind the antibiotic with an affinity that is independent of the overall base composition. It is possible that actinomycin D is intercalated between successive planes formed by hydrogen-bonded base pairs of the primer DNA. Actinomycin can be dissociated from the denatured DNA at temperatures which cause uncoiling of the helical regions. So the comparative insensitivity of DNA polymerase to actinomycin action may be due to denaturation or separation of strands of the primer DNA which may occur as a prerequisite for replication. This then would preclude actinomycin binding and DNA polymerase may preferentially use these previously denatured regions or the denaturation itself may be caused by a 'depolymerase' present in the DNA polymerase preparation [Lehman, I. R., *Fed. Proc.*, **21** (1962), 378]. On the other hand, the specific sensitivity of RNA polymerase may be due to its utilization of native DNA as primer which does not suffer any alteration in secondary structure so as to cause a dissociation of the actinomycin DNA complex. This then would easily explain the replication of RNA virus infecting host cells in the presence of actinomycin which virtually inhibits any RNA synthesis by the host cell. But the viral machinery to synthesize RNA is by an RNA-dependent RNA polymerase referred to as ' RNA synthetase ' which is qualitatively different from DNA-dependent RNA polymerase.

While it is true that actinomycin D causes almost complete inhibition of RNA synthesis, there is a small residual precursor incorporation into RNA which does take place independent of the antibiotic concentration employed. Of all species of RNA studied, precursor incorporation into S-RNA is inhibited to a lesser extent as compared with its actinomycin effect, say on ribosomal RNA synthesis. The residual incorporation has been accounted for by the turnover of the terminal CpCpA residues of S-RNA. The enzyme responsible for this terminal incorporation is insensitive to actinomycin [Franklin, R. M., *Biochem. biophys. Acta*, **72** (1963), 555], but then this terminal incorporation does not represent true RNA synthesis. So the concept that all DNA-dependent RNA synthesis is inhibited by actinomycin may be taken to have been established beyond doubt and this occurs primarily by the binding of actinomycin to primer DNA.— G. PADMANABHAN

Drug requiring phase in the growth of enteroviruses

H. J. Eggers and I. Tamm (8th International Congress for Microbiology, Montreal, 1962, Abstracts of Papers, p. 85) and H. J. Eggers [*Cold Spring Harbor Symposium on Quantitative Biology*, **27** (1962), 309] have recently shown the phenomenon of drug dependence in viruses also. H. J. Eggers and I. Tamm [*J. exp. Med.*, **113** (1961), 657; *Virology*, **15** (1961), 65; **20** (1963), 62], B. Loddo [*Boll. Soc. ital. Biol. sper.*, **38** (1962), 8] and D. Crowther and J. L. Melnick [*Virology*, **15** (1961), 65] have demonstrated that 2-(α-hydroxybenzyl)-benzimidazole (HBB) and guanidine specifically inhibit the reproduction of enteroviruses, while some variants of this group requiring HBB or guanidine for multiplication have been isolated. The single cycle growth characteristics of drug dependent virus growing in the presence of the drug are similar to those of the drug sensitive parent virus growing in the absence of the compound. Further, the drug concentrations required for maximal growth of dependent mutants are strikingly similar to those causing marked inhibition of the sensitive parent viruses, thereby suggesting that at the same site of action dependence and sensitivity involve opposite drug effects.

H. J. Eggers, E. Reich and I. Tamm [*Proc. nat. Acad. Sci., Wash.*, **50** (1963), 183] have reported the kinetic and biochemical experiments on the drug requiring and drug sensitive phases in the growth of viruses. Cosackic A9 virus (Woods strain) and its HBB dependent variant, grown in monkey kidney cells and poliovirus (Brunhilde strain) and its guanidine dependent varient, grown in Hela cells, were employed in the studies. The HBB dependent cosackic A9 virus was assayed in the presence of 22 μg./ml. of HBB and the guanidine dependent poliovirus in the presence of 100 μg./ml. of guanidine hydrochloride.

The results of experiments carried out to determine exactly the HBB requiring phase in the growth cycle indicate that HBB requiring phase begins in the second half of the latent period. Similarly, it has been found that the HBB inhibitable phase of the HBB sensitive parent virus begins in the second half of the latent period and the duration of the HBB requiring phase extends from the beginning of the second half of the latent period well into the exponential increase phase. Similar result is observed in the case of HBB sensitive phase.

The requirement of HBB for the synthesis of the infective viral RNA of HBB dependent virus has been demonstrated and confirmed by studying the incorporation of uridine-H^3. The RNA of the HBB sensitive virus cannot replicate in the presence of uridine-H^3. Similarly the RNA of the guanidine dependent poliovirus requires the presence of guanidine for its replication, while the virus multiplication and viral RNA synthesis are completely inhibited by guanidine in the case of guanidine sensitive virus.

These results are compatible with the hypothesis that the drug dependent and drug sensitive processes are biochemically analogous. Support for this hypothesis comes from the observation that RNA polymerase activity is demonstrable in Hela cells infected with poliovirus but not in uninfected cells [Baltimore, D., Eggers, H. J., Franklin, R. & Tamm, I., *Proc. nat. Acad. Sci., Wash.*, **49** (1963), 843]. HBB and guanidine inhibit the RNA polymerase activity in cells infected with drug sensitive virus and do not inhibit the enzyme in drug dependent mutants. These observations support the hypothesis that HBB and guanidine have direct effects on the synthesis of virus induced RNA polymerase and thereby affect the replication of viral RNA and also support the inference that the virus induced RNA polymerase is the enzyme system responsible for viral RNA synthesis. However, the nature of the HBB insensitive early process in enterovirus growth is not clear.— S. RAMANATHAN

Protein synthesis by reticulocyte ribosomes

Chloramphenicol, used as an inhibitor of protein synthesis both in intact cells and cell-free systems, is known to interfere in the last step, viz. transfer of SRNA-amino acid to the ribosomes. In mammalian systems, however, its adverse effects are noticed only in the cell of the haematopoietic system resulting in anaemia, leukopenia, thrombocytopenia or aplastic anaemia. While the mechanism of this toxicity is not clear, there is evidence that the antibiotic affects the primitive or immature cells during the maturation stage. If the maturation steps require synthesis of ribosomal template RNA directing haemoglobin synthesis, the drug might interfere at some step in this process. Using poly U as a messenger RNA for the incorporation of phenylalanine into polypeptide chains by reticulocyte ribosomes as a model for protein synthesis, the effect of chloramphenicol on this process has been investigated [Weisberger, A. S., Armentrout, S. & Wolfe, S., *Proc. nat. Acad. Sci., Wash.*, **50** (1963), 86]. It has been established that the messenger RNA attaches itself to the ribosomes, resulting in the formation of aggregates which represent the functional unit in protein synthesis. The antibiotic could act either at this stage of attachment or it combines with the ribosomes, thus preventing aggregation or it affects the messenger RNA itself.

Chloramphenicol at low concentrations was found to inhibit the formation of C^{14}-labelled phenylalanine induced by poly U and further the inhibition was dependent on the presence of the antibiotic before the poly U could react with the ribosomes and phenylalanine. This suggests that once the messenger was attached to the ribosomes the antibiotic was without effect. Whether this involved interaction of poly U or the ribosomes with chloramphenicol was, however, not clear. Earlier, messenger RNA had been fractionated into four fractions, one of which (23-30 S) had the specific ability to combine with the ribosomes to form the aggregate [Ishihame, A., Mizuno, N., Takai, M., Otaka, E. & Osawa, S., *J. mol. Biol.*, **5** (1962), 251] and addition of chloramphenicol inhibited the formation of this active fraction of mRNA. The quantitative aspects of the inhibitory activity of the antibiotic further indicate that the inhibitory effect becomes apparent when the drug combines with or inactivates on an average one of three unidylic acid residues of poly U at random.

From studies on the conformation of chloramphenicol in solution based on NMR and Raman spectra, it has been shown [Jardetzky, O., *J. biol. Chem.*, **238** (1963), 2498] that the active D(−)-threo isomer bears a striking resemblance to UMP in size, orientation of the individual moieties and distribution of electronegative groups. If it is assumed that this similarity has a bearing on the mode of action, then some features of the structure-activity relationships in this series can be understood. Any alteration of the propanol moiety would destroy the similarity to the ribose ring and any change in the size of the dichloracetamide side chain would alter the resemblance to the phosphate. Studies on the effect of substituents in these positions also show that the derived analogues are devoid of antibacterial activity. The other three isomeric forms of chloramphenicol, viz. L(+)-threo, D(−)-erythro and L(+)-erythro, cannot form nucleotide-like conformations. The results of studies, whether the antibiotic is specific for poly U or is effective for other nucleotides as well, will, therefore, be of considerable interest. However, since our present concept of protein synthesis visualizes similar mechanisms as operative in bacterial and mammalian systems, these observations do not explain the selective toxicity of the drug to bacterial systems.—(Miss) M. PREMA BAI

Ribosomal particles and polypeptide synthesis

There is abundant evidence to establish that ribosomes are the main sites of protein synthesis. Originally it was postulated that the ribosomal RNA was the template for amino acid sequence during polypeptide formation. Now it is well known that an additional RNA, mRNA — a messenger — is required to transmit the genetic information on to sRNA so that the latter can assemble in order the amino acids into proteins. New insight into these molecular processes which take place on the ribosomal surface is gained by the recent studies presented independently and almost simultaneously by A. Gierer [*J. mol. Biol.*, **6** (1963), 148], by J. R. Warner, P. M. Knopf and A. Rich [*Proc. nat. Acad. Sci., Wash.*, **49** (1963), 122], by F. O. Wettstein, R. Staehelin and H. Noll [*Nature, Lond.*, **197** (1963), 430] and by T. Staehelin, F. O. Wettstein and H. Noll [*Science*, **140** (1963), 180] as a result of which the functional unit of protein

synthesis has been shown to be the ' ribosomal aggregates ', ' ergosomes ' or ' polysomes '.

Though ribosomes from different sources were found to exist in different states of aggregation, the significance of these subunits in this ' tape mechanism ' of protein synthesis was unknown. Earlier contributions dealing with the involvement of ribosomal particles came from Watson's laboratory [Tissiers, A., Schlessinger, D. & Gross, F., *Proc. nat. Acad. Sci., Wash.*, **46** (1960), 1450; Risebrough, R. W., Tissiers, A. & Watson, J. D., *Proc. nat. Acad. Sci., Wash.*, **48** (1962), 430]. It was shown that an active fraction differs from an inactive one in its high stability at low Mg^{2+} concentrations and its higher sedimentation coefficient. These differences in activity were attributed to the increased molecular weight of the ribosomes caused by mRNA binding and also the possible aggregation of ribosomes.

The sedimentation patterns of freshly prepared ribosomes showed at least three fractions: the main fraction with 70s-80s, a slow-moving fraction with 40s-60s and a fast-moving fraction with 120s-220s. The main fraction of ribosomes with sedimentation coefficient of 78s and 80s was considered to be the ribosomal unit taking part in protein synthesis. During the lifetime of mRNA molecule *in vivo*, it is closely attached to ribosomes taking part in protein synthesis. All the ribosomes are not in a steady state at all times, but are in a continuous state of assembly and breakdown during any one moment. Site distribution of aggregates at the time of protein synthesis depends upon the lifetime of mRNA. T. Staehelin, C. C. Brinton, F. O. Wettstein and H. Noll [*Nature, Lond.*, **199** (1963), 865] have isolated the following four groups of potentially functional 70s particles from *Esch. coli* which reflect the different phases of ergosome assembly and breakdown: (a) Vacant monomer particles released during protein synthesis *in vivo*, which show characteristic tendency for dimerization and make up a steady state pool in the cell and are capable of accepting mRNA. (b) Monomers to which a finished peptide chain is attached; this class of monomers accumulate during protein synthesis. These with ' release factor ' are converted to monomer (a) which accept mRNA. (c) Monomers containing both unifinished peptide chain and fragments of mRNA. These result during the isolation procedure due to cleavage, by RNAase, of bonds within the exposed stretches of mRNA that connect the 70s particles. (d) Monomers attached to the end of a nascent mRNA or partially combined with the RNA template. This has been considered to be the hypothetical complex which represents the initial step in the assembly of ergosomes *in vivo*.

A. Gierer [*J. mol. Biol.*, **6** (1963), 148] has advanced two hypothetical models using the ribosomal particles as the ' work-bench ' for protein synthesis. In model 1, mRNA is statically linked to the ribosomal surface. Here only one ribosome would contain as many sites as amino acids necessary for the polypeptide. The growth of the peptide chain by one amino acid is accompanied by a shift of the peptide chain from one active site to the next on the ribosomal surface, and in the process the growing polypeptide point is attached to the next group of nucleotides of mRNA. The growing peptide needs to be attached to the ribosomal particle at the point of growth or active site only and since there are a number of active sites on the ribosomal particles, several peptide chains can be simultaneously formed on the same ribosome unit.

The second model has a direct bearing on the results obtained by Gierer with reticulocytes. In this, the mRNA is not statically linked to the ribosomes, but is attached by a small group of nucleotides to the ribosomal surface. There is only one site or very few sites of synthesis on the ribosome to which the peptide chain can be attached. The mRNA is shifted across the site from one coding group of nucleotides to the next, whenever the growing chain is extended by one amino acid. This mechanism is well illustrated in a paper by W. Gilbert [*J. mol. Biol.*, **6** (1963), 389]. An amino acid is first activated and then transferred to a specific sRNA by a specific enzyme, which leaves the amino acid bound by an ester linkage. An attack by an amino acyl-sRNA on the ester linkage joining the polypeptide chain to its terminal sRNA splits off the sRNA that was previously on the end of the chain and leaves the chain bound to the new amino acid and the new sRNA The specificity of this process is dictated by mRNA. Thus sRNA must have a site capable of holding the sRNA-polypeptide. It must have also a structure that holds the messenger, so that a new amino acyl-sRNA is forced to base pair correctly, in order to bring its amino acid to the active site when the peptide bond is formed. The sRNA that was at the end of the chain is ejected and the chain will end in a new sRNA. During this ejection the new sRNA will move to the site that the old sRNA had occupied. This site is in a way an ' exchange site '. This motion of sRNA, as it slips into the site and displaces the previous occupant, forces the mRNA to move simultaneously over the surface of the ribosome. At the end of the process, the sRNA-polypeptide still persists at the original site on the ribosome, where the sRNA is hydrogen-bonded to the messenger. After the movement of the messenger by one reading unit over the surface of the ribosome, the messenger is now in such a position that it facilitates the incoming sRNA to hydrogen bond correctly and the amino acid is properly placed in the sequence. As this process continues, the polypeptide chain grows and ribosomes move along the messenger. Eventually, the leading end of the messenger gets far enough away from the ribosome unit, so that a second ribosome unit can attach to it. Then a second polypeptide chain is begun and the second ribosome moves along the messenger by the above reading device.

sRNA binding to ribosome is non-specific. These bonds are probably Mg^{2+} bridges to ribosomal RNA and possibly hydrogen bonds to the common terminal C-C-A group. Specificity is imposed by the messenger, the hydrogen-bonded fit between complementary bases, and the incoming sRNA acts as the wands of a lock to permit only the correct sRNA to slip into place. After the movement of mRNA accompanied by peptide

bond formation, the sRNA now bound covalently to the chain and by the Mg^{2+} bridges to the ribosomes, pins the messenger against the ribosomes by these same hydrogen bonds. The messenger is also held by the Mg^{2+} bridges to the ribosomal structure, the hydrogen bonds making this overall fit possible. This fit preserves the register between the polypeptide chain and the messenger.

Though this hypothesis provides a role for the complicated structure of the ribosomes, a lot of experimental evidence is necessary to obtain a clear picture of the 'tape mechanism' of protein synthesis taking place on the ribosomal surface. But it is certain that the ribosome "is a non-specific work-bench, which holds the messenger, the growing peptide chain, the amino acyl-sRNA and the necessary enzymes in correct position for the complicated formation of a peptide bond".

It will be of interest to know how this tape mechanism can allow for the synthesis of complete protein molecules, especially in the context that polyribosomes of the order 200s have been attributed as active units in protein synthesis but not the 70s units.—T. ANANTHASAMY

Progress Reports

National Chemical Laboratory, UK

The report of the National Chemical Laboratory, UK, for the year 1962 (HM Stationery Office, London, 1963; pages 91; price 6*s.* 6*d.*) gives an account of the work carried out at the laboratory in its six research groups. Several new projects that hold considerable promise have been started, e.g. the application of high-temperature flame technology in mineral processing, solid state problems in inorganic chemistry and thermodynamic properties of non-stoichiometric compounds.

Work on the field-emission and field-ion microscopy was continued in the Director's Research Unit and it has been shown that while tungsten offers a suitable substrate on which body-centred cubic metals can grow epitoxially, platinum may be a suitable substrate on which face-centred cubic metals (e.g. nickel) can grow; work has, therefore, been started on the preparation of clean platinum tips.

The Chemical Thermodynamics Group continued its work on obtaining values for thermodynamic properties of compounds by statistical calculations, measurement of heat capacities and determination of heats of formation. For calculating heats of formation, a new bond energy scheme has been developed from the premise that the energy of a C–X bond depends on the hybridization state of the carbon atom. During the year a new programme has been started to study the lower iron phosphides, Fe_3P and Fe_2P, and the solid solution of phosphorus in iron at elevated temperatures. Construction of an apparatus which employs a thermobalance to record the weight loss *in vacuo* from a Knudsen effusion cell with an orifice of known dimensions has been completed. A study of the thermodynamic properties of non-stoichiometric compounds has been started and a solid state electrochemical cell has been constructed for determining the free energies of solution of oxygen in non-stoichiometric oxides. A colour reaction for certain phenols has been developed. The test consists in nitrosation of the phenol followed by the addition of an alkaline sodium nitroprusside solution.

The New Materials Group continued its efforts towards the preparation of new materials with unusual and potentially valuable properties. Several different reactions have been studied to prepare simple compounds and polymers containing aluminium-nitrogen bonds. The most interesting results have been in the case of reactions between triphenyl aluminium and various primary amines in benzene or toluene solution when tetramers of the type $(C_6H_5N.Al.C_6H_5)_4$ have been obtained. With a view to synthesizing polymeric semiconductors, a series of charge-transfer complexes have been prepared from strong electron acceptors, e.g. tetracyanoethylene and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. A number of polymeric redox compositions (electron-exchange polymers) have been prepared in the form of beads, granules, sheets or membranes. Such compositions have been prepared from cellulose or polyvinyl alcohol and a redox polymer in a finely ground state. Studies on ion-exchange membranes with regard to their selective-permeability behaviour have been undertaken with a view to finding the effects of membrane structure on selective behaviour towards particular ions, and of finding how ion-exchange membranes can be used in separation processes.

The Extraction of Metals Group has directed attention to a number of problems basic to the hydrometallurgical and some electrochemical industries, and has worked out some new experimental techniques such as the rotary contactor for solvent extraction from pulps, and flame technology applied to refractory minerals. The study of the phase changes induced in beryl by its passage through a high-temperature flame marks the beginning of a major project to explore the use of such flames in metallurgy and mineral processing. Equipment is being installed which will permit the production of flames with temperatures up to 15000°C. The group also carried out work for the UK Atomic Energy Authority on the development of a contactor which enables solvent extraction processes to be performed in the presence of solids, the preparation of an anion-exchange resin from polyvinyl chloride for the recovery of uranium from leach liquors, and the extraction of beryllium from flotation concentrates of beryl. An anion-exchange resin from PVC has been made for the absorption of uranium from leach liquors. A process has been developed for the extraction of beryllium in which finely divided beryl is blown through a hot flame at 3000°; fusion of the particles occurs and on leaving the flame these are rapidly quenched to an X-ray amorphous glassy material. It is thus possible to fuse and quench individual beryl particles with the minimum of interaction with accompanying gangue material.

In the Inorganic Chemistry Group, interest has shifted to solid state problems. The catalytic properties of europium oxide have proved of interest. The reflectance spectra of rare earths are

characteristic of the immediate environment of the rare earth ions and have been found to be of use in supplying information regarding any variation of the local electric field. The preparation of lanthanon selenides of the highest possible purity, particularly in regard to freedom from oxygen, is being attempted. The method involves conversion of the oxides to the anhydrous chlorides which are in turn converted to the selenides. The purification of certain elements likely to be of interest as semiconductors, e.g. bismuth, tellurium, antimony, indium, gallium, aluminium and mercury, has been carried out. Materials which may find use as optical masers have been studied with regard to their preparation and analysis. Preparation of pure alumina via ammonium alum for the production of rubies by the flame-fusion process and purification of calcium fluoride have been carried out.

Research in the Corrosion of Metals Group during the year has been concentrated on a limited number of problems of ferrous corrosion, corrosion in flowing water, passivation or inhibition and the specific role of the anions present in a corrosive solution, and anaerobic corrosion in soils and polluted waters. Work has continued on the protection afforded in flowing systems, by the films laid down when very small additions of carbonates, silicates are made to the water. Work has been started on the chemical nature and morphology of the corrosion products laid down under different conditions. The role of phosphate as a corrosion inhibitor has been studied by measuring the uptake of radioactive phosphate ions by the oxide film on an iron surface under different electrochemical conditions. In the work on microbiological corrosion, corrosive activity has been found to be related to the reproductive and metabolic activity of bacterial cultures. Corrosion is considered to be promoted by a cathodic depolarization mechanism which is primarily a problem of the enzyme chemistry of the bacteria. Some progress has been made in the understanding of the nutritional processes of the organisms and their utilization of sulphate.

Announcement

▪ *Award of doctorate degrees* — The following candidates have been declared qualified for the award of Ph.D. degree for the theses shown against their names within parentheses:

Delhi University: Kamal Nain Mehta (*Some aspects of hydromagnetic flows through porous-walled channels*); Harish Chandra Malhotra (*Kinetics of degradation of pyrophosphates*); Geeta Chakrabarty (*A study of cyanomaelurin and some naturally occurring flavonoid compounds*); M. R. Vijayaraghavan (*Morphological and embryological studies on the families Actinidiaceae, Chloranthaceae and Ranunculaceae*); Kusum Kanta (*Intraovarian and test-tube fertilization in some Angiosperms*); Shyam Sunder Jalan (*Morphological, anatomical and embryological studies on some Ranales*); Sipra Guha (*Experimental studies on Allium cepa*); Prakash Chandra Jain (*Interactions of negative K-meson with nuclei in photographic emulsion*); Narinder Nath Bhandari (*Embryological investigations on the families Ranunculaceae, Winteraceae and Magnoliaceae*); and Subhash Chandra Saxena (*Adaptive modifications of certain Indian hill stream fishes*).

Mysore University: B. N. Chowdaiah [*Cytology of some Indian Diplopoda (Myriapoda)*].

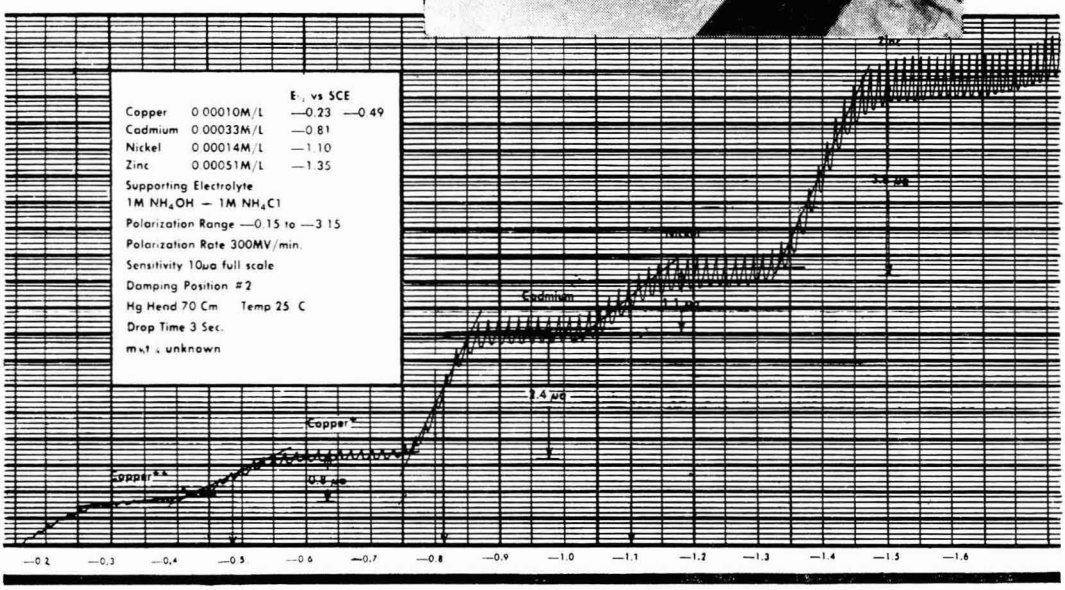
Panjab University: Sant Singh Pahil (*Strength of sulphonic acids and their use as titrants in non-aqueous media*); Dasondha Singh (*Cytomorphological studies in some Indian members of Thelypteridaceae and the genus Dryopteris*); Jagdish Chandra Sharma (*Age changes in bodily proportions in Maharashtrians*); Inder Raj (*Synthetic investigations in terpenoids*); Lekh Vir (*Cosmic ray variations with time*); and Raj Kumar Sharma (*Thermodynamic properties of solutions of poloxyethylene glycols in polar and non-polar solvents*).

Poona University: Amar Singh Gulati (*Synthesis using phenolic components of cashewnut shell liquid*); R. B. Mawal (*Studies in milk proteins with special reference to beta-lactoglobulins*); G. P. Thakar (*Complex metal hydrides in organic chemistry*); and A. G. Kulkarni (*Studies in strong electrolytes*).

Saugar University: Ayodhya Prasad Shrivastava (*Solid state studies in high polymers with special reference to polythene and polymethyl methacrylate*).

Sri Venkateswara University: Mohammed Habibulla (*Studies on the neurosecretory system of an arachmid, Heterometrus swammerdami*); and R. V. Krishnamoorthy (*The charge properties of cell contents in relation to the hydrogen ion concentration*).

RECORDING ELECTRO-POLARIZER



		$E_{\frac{1}{2}}$ vs SCE
Copper	0.00010M/L	—0.23 —0.49
Cadmium	0.00033M/L	—0.81
Nickel	0.00014M/L	—1.10
Zinc	0.00051M/L	—1.35

Supporting Electrolyte
1M NH_4OH — 1M NH_4Cl
Polarization Range —0.15 to —3.15
Polarization Rate 300MV/min.
Sensitivity 10μa full scale
Damping Position #2
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Drop Time 3 Sec.
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