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Journal of Scientific & Industrial Research

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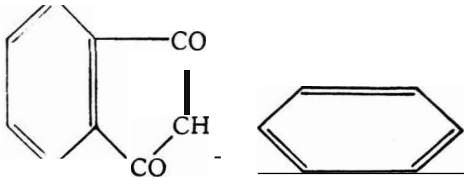

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INDEX TO ADVERTISERS

Current Topics

Recruitment of Scientific & Technical Personnel

AN interim report of a survey conducted recently by the Directorate of Scientific & Technical Personnel, Council of Scientific & Industrial Research, on the employment opportunities for scientific and technical personnel in India during 1967 deserves attention for several reasons. Besides providing an idea of the existing job availability pattern for scientific and engineering personnel, the survey serves to indicate the need for a coordinated and concerted approach to the important problem of utilization of scientific and technical manpower in the country.

For the purpose of the survey, the existing vacancies as well as those likely to be created during 1967 in the existing establishments are considered to reflect the employment opportunities directly. The requirement of personnel for new organizations for departments likely to come into being during the year — an uncertain factor — has not been taken into account. The report provides statistics not only with regard to the number of unfilled posts but also the time lag in filling them.

Among the establishments covered under the survey, the largest number of unfilled posts is reported from agricultural universities (30 per cent), followed by institutes of higher technology (27 per cent), mineral survey and development departments (25 per cent), engineering colleges (20 per cent) and research organizations (19 per cent). Two important findings emerging from the survey are noteworthy. More than 50 per cent of the vacancies have remained unfilled for periods exceeding a year, and the delay in filling vacant posts is generally more for the senior posts rather than for the junior posts. The survey also reveals that about 37 per cent of the total vacancies in postgraduate science departments in universities remained unfilled for over a year. Subjectwise, nearly 60 per cent of vacancies for senior posts in physics, chemistry and botany have remained unfilled for long. In the public sector industrial establishments nearly 7 per cent of the posts are unfilled both at junior and senior levels, while in the private sector the number is negligible.

Delays in the filling up of sanctioned vacant posts, particularly at the senior level, is a matter for concern. Leaving posts unfilled for long in universities, research organizations and institutes of technology must inevitably have serious repercussions on both teaching and research. Much importance is given at present to agriculture and exploitation of the country's mineral resources in making the country self-sufficient in food and for expanding our export trade of minerals. It is, therefore, disturbing to see that the work of the organizations concerned with these important fields is allowed to suffer through failure to fill senior posts promptly. Lack of funds is evidently not the main factor impeding the speedy filling up of the posts, since the survey is concerned only with sanctioned posts for which funds are earmarked. The inevitable conclusion is that the delays are due perhaps to procedural formalities. Delays may also be due to laying down of stringent and specific job requirements and experience for senior posts, with the result that persons with 'tailor-made' qualifications are not available. It may be that there are other factors responsible for this situation which cannot be spelt out. Whatever be the causes responsible for the present state of affairs with regard to recruitment of personnel to fill up the posts, a determined approach is called for to find suitable remedial measures.

To find personnel with all the requisite qualifications for the vacant jobs is not only not easy but wellnigh impossible. Personnel for teaching positions in universities and higher technological institutions must be found by the institutions themselves by instituting long-term and continuing programmes of selecting and training personnel from among the promising postgraduates with a flair for teaching. For research positions and for personnel trained in mineral prospecting and development, the establishments concerned should look for persons with basic qualifications and provide the necessary in-service training facilities. The example of the Bhabha Atomic Research Centre in this regard may be worth emulating.

Noise Survey in Calcutta

M. PANCHOLY, A. F. CHHAPGAR & S. P. SINGAL
National Physical Laboratory, New Delhi 12

NOISE not only interferes with speech communication, social activities, efficiency of work and enjoyment of rest but also has other adverse effects such as impairment of hearing, nervous strain and annoyance. In recent years, considerable amount of work has been done on this subject. In India, results of noise studies in some cities published[1-3] by the National Physical Laboratory have aroused considerable interest in the public mind and created an awareness of the need for noise control measures.

The object of noise studies is generally to assess the disturbing values of the prevailing noise levels and help formulate appropriate noise reduction measures. Since the character of noise varies according to place and time, the results of a survey carried out at a certain time and place cannot be generalized to apply to other localities and it is necessary to evaluate each case separately. Following the studies in Bombay and Delhi, a similar survey in Calcutta was, therefore, undertaken at the instance of, and in collaboration with, the Citizens Club of Calcutta. In planning this work the experience of the previous studies and recent developments in the subject were kept in view.

The survey included: (i) day-time noise levels in residential areas, shopping areas, commercial areas, recreational areas, hospital areas and areas containing educational institutions; (ii) night-time noise levels in residential areas; and (iii) frequency analysis of the prevailing noises.

The measuring technique was, in general, the same as reported in the earlier paper[1].

Noise Criteria for Annoyance

Recent work on the subject has shown that annoyance due to noise does not depend on sound intensity alone but also on its other physical characteristics as well as on subjective reactions and psychological factors. Some of these factors include the time element (day or night), character of noise (non-impulsive or impulsive), composition of noise (wide frequency range or containing distinct frequency components), duration of noise (continuous or intermittent), environments (indoors or outdoors), the purpose for which the locality is used (residential or commercial), previous conditioning of the subject, present mood of the subject, and so on.

In general, the subjective annoyance value of a noise can be quantitatively described by its 'noise rating' which is derived from a family of frequency versus loudness curves indicating the subjective equivalent of the noise level or the 'noisiness' of noises of various types. The determination of the annoyance value by this method is rather involved and, for most practical purposes, can be replaced by the measurement of the sound pressure level on the '*A*' weighting network. For, it has been found by experiments that the '*A*' level generally corresponds to a good compromise between the annoyance curves of octave bands having centre frequencies of 500, 1000 and 2000 c/s. Thus this simple, practical and objective measurement serves reasonably well to measure the subjective factor of noise annoyance.

Noise rating figures as related to subjective annoyance have been arrived at on the basis of the work carried out in UK, Germany, USA and elsewhere and maximum permissible limits of noise in various situations have been suggested[4,5]. According to one suggestion, which is fairly representative, the basic permissible noise level limit in front of residential buildings is to be 45 db.*A* during day-time and 35 db.*A* during night-time. This is based on the assumption, corroborated by measurements[2], that an average house provides a sound insulation of 5 db. with windows open and 10 db. with ordinary windows closed. The prevailing noise levels should not exceed these limits. It is, however, necessary to apply certain corrections to the measured noise levels to account for the various subjective factors discussed earlier.

Day-time Noise Levels

From the detailed results of the survey, summarized in Table 1 and indicated in Fig. 1, it is seen that the average day-time '*A*'-weighted noise level is between 70 and 75 db.*A* in localities with medium to heavy traffic and between 50 and 70 db.*A* in localities with less vehicular traffic. In certain localities with little traffic but having specific noise sources like noisy trades, electric substation, loudspeakers, etc., the level does not go below 65-70 db.*A* and sometimes remains as high as 80 db.*A*.

Night-time Noise Levels

The night-time noise levels generally show a drop of 10-15 db. from the day-time levels, the average prevailing levels ranging between 45 and 60 db.*A*. The indoor noise levels at night-time are, therefore, likely to be 5-10 db. lower depending on whether windows are open or not.

Discussion

Comparing these observed noise levels with the criteria mentioned earlier, it is seen that in all the localities the measured noise levels are considerably higher than the values recommended, both for day-time as well as for night-time. In fact, the measured noise levels at night-time, except in a few quiet localities, are even higher than the recommended day-time noise levels. Surveys conducted elsewhere on the possible community reaction to prevailing noise levels indicate that the degree of reaction depends on the extent by which the above criteria are exceeded. The measured noise levels in most residential localities in the present survey

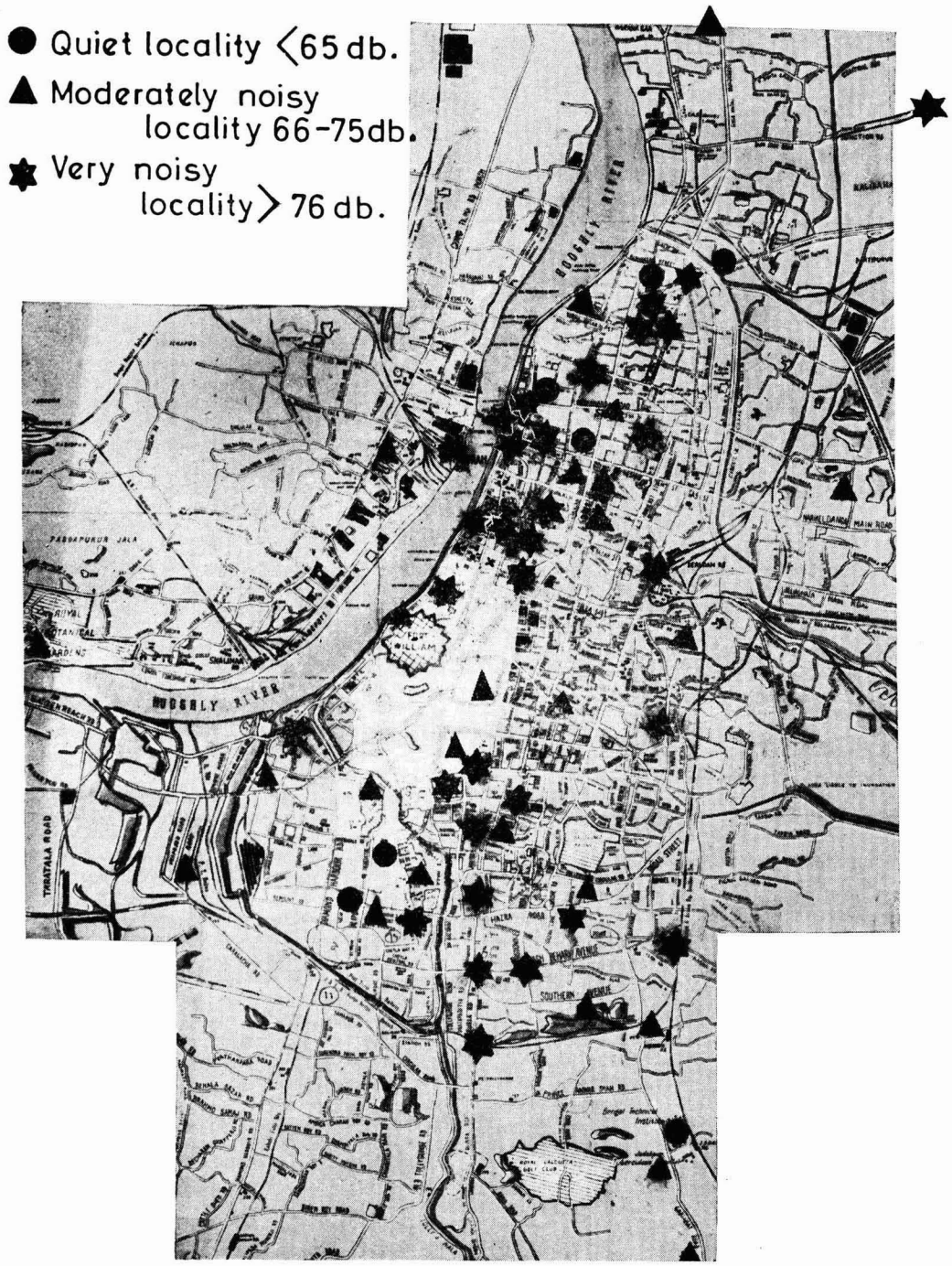

Fig. 1 — Map of Calcutta and Howrah indicating the distribution of noise levels

TABLE 1 — VALUES OF TYPICAL NOISE LEVELS IN SOME SELECT LOCALITIES IN CALCUTTA

Type of locality	Noise level in db.*A*			Percentage of time during which average level persists	Remarks
	Max.	Min.	Av.		
Locality with heavy traffic during day-time	79	69	72	45	Cars, buses, trams
Locality with medium traffic during day-time	77	62	68	46	Cars, buses, trucks
Locality with light traffic during day-time	59	54	56	67	Noise from birds
Locality with small workshops or factories	81	64	70	61	No vehicular traffic
Locality with electric substation	79	76	78	95	No vehicular traffic
Locality with loudspeaker blaring	80	68	73	38	Pedestrian traffic
Recreational locality	71	60	63	66	Noise from birds
Typical night-time level	54	50	51	75	—

during day-time are higher than the suggested maximum permissible limits by 20-25 db. At night also the measured levels are 15-20 db. higher. Normally, the community reaction to this would be intense. Even assuming extreme preconditioning of the affected population to this noise, the reaction is likely to be widespread complaints.

Possible Remedies

There are certain possible remedial steps that may be effective in dealing with the problem. Noise levels can be brought down by concerted action taken by the citizens, local authorities, planning authorities, etc. The steps required to be taken are: (a) to limit existing noise levels, (b) to prevent further growth of noise levels and (c) to avoid objectionable noise in developing localities.

For noise in existing residential localities the steps which may be considered necessary are to stop or reduce existing noise sources by removal or structural screening, to remove or restrict noisy trades, to create a silence zone as far as sounding of car horns is concerned, to restrict or regulate through traffic in residential localities and to regulate the intensity and time for using loudspeakers, whether static or mobile.

Steps for preventing further growth include, in addition to the above, restrictions on noise generated by individual automobiles and segregation of trading and business areas from residential areas. Zoning of residential localities, suitable orientation of buildings with respect to roads carrying heavy traffic and adequate set-backs are also recommended[6].

The problem of developing localities is comparatively easier if the town planners take into account the above suggestions while planning for the future.

Summary

A detailed survey of day-time and night-time noise levels in various parts of Calcutta has been made. Some possible remedial measures to deal with the problem of noise have been indicated.

Acknowledgement

The survey was planned at the instance of, and aided by, Citizens Club, Calcutta, and the authors wish to acknowledge their active cooperation in the work. The authors are also grateful to the police authorities of Calcutta who provided all facilities and help during the survey.

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Thirty-third International Foundry Congress

P. K. GUPTA
National Metallurgical Laboratory, Jamshedpur

FOUNDRY experts from twenty-eight nations assembled for the first time in India, to take part in the Thirty-third International Foundry Congress. The congress has so far been held annually in different countries, which are highly developed and industrially advanced. The change of venue represents the realization of the necessity of economic build-up of the developing countries speedily and efficiently. It is also a recognition of the role of the developing countries in the growth and development of industrial technology, particularly production metallurgy and foundry techniques.

Over 700 delegates comprising scientists and foundry technologists from Austria, Belgium, Brazil, Bulgaria, Chile, Congo, Czechoslovakia, Costa Rica, Denmark, Finland, France, Germany, Great Britain, Hungary, India, Iran, Italy, Japan, Nigeria, Netherlands, Poland, Philippines, Switzerland, Sweden, Turkey, USA and USSR took part in the deliberations of the congress. The United Nations Team for Industrial Development was led by Dr B. R. Nijhawan.

The Institute of Indian Foundrymen made extensive and elaborate arrangements for the inaugural and technical sessions.

The congress, held at Vigyan Bhavan, New Delhi, during 4-9 December 1966, was inaugurated by the Vice-President, Dr Zakir Hussain, who deputized for the President, Dr S. Radhakrishnan. The inaugural session was presided over by Shri D. Sanjivayya, Union Minister for Industry.

Speaking at this session, Mr W. E. Huber, President of the Congress, who is also the Managing Director of Sulzer Brothers, Switzerland, said that it was indeed a remarkable occasion that for the first time foundry experts from so many different countries had met outside of Europe and North America to discuss problems of the foundry industry. Mr Huber referred to the excellent quality of Indian iron ore and observed that the present and future demands for increased productivity could be met only if the metallurgical and technological developments of metal casting kept pace with technical developments in general. The advances made in many fields are no longer the outcome of mere chance but the results of intensive research. However, the human aspect was just as important as the technical and material considerations, and one could not afford to ignore training of a new generation of foundrymen. Efforts must be made to improve the working facilities and conditions of foundrymen and there was still much to be done in this area.

Welcoming the delegates, Dr B. R. Nijhawan, President of the Institute of Indian Foundrymen, pointed out that the venue of the International Foundry Congress in the preceding years had always been in a highly developed and industrially advanced country, and the change of venue was a true recognition of the significance, importance and the necessity of accelerating the rate of economic growth and industrial advancement in the developing countries. Dr Nijhawan said: "The Centre of Industrial Development in the United Nations, apart from its enterprising and pioneering work in the field of industrial development of developing countries, has recognized the need and value of actively participating in international conferences, such as the International Foundry Congress, which provide platforms for the efficient transfer of technical know-how from the highly developed to the developing countries, and enable them to mutually understand their problems of economic growth and industrial development. The exchange of technical know-how and interchange of ideas on foundry technology, which this congress will undoubtedly promote, will form an important nucleus for the industrial growth and economic development of developing countries and will indeed be valuable, adjudged by any standard, national or international."

Discussing the problems confronting the foundry industry in the developing countries, Dr Nijhawan said the chief ones are: (i) the procurement of imported capital plant and equipment involving heavy outlay of foreign currency; (ii) short supply of machinery spares and plant accessories; and (iii) lack of technically trained personnel. The developing countries had to choose a technology not necessarily the best and the most up-to-date one, but one which would fit in well with the overall pattern of their industrial growth and economic stature, and is more suited to their specific market trends and consumer needs.

Technical Sessions

Thirty-four technical papers from foundry experts specializing in different areas and eight papers from the United Nations Expert Team were presented and discussed in 10 technical sessions.

Moulding and Mould Materials

Seven papers were presented and discussed on the subject in two sessions held under the chairmanship of Dr D. V. Atterton (UK) and Mr G. Greig (UK).

Dr Von Paavo Asanti (Finland) recommended the use of chromite and olivine in preference to quartz sand for moulds in the production of unalloyed and highly alloyed steels. On quartz base, in oxidizing atmosphere, strong chemical reaction and penetration have been observed; these are less pronounced on olivine and chromite bases. Very heavy burn-on of 13 per cent Mn steel has been observed in the quartz sand moulds; in moulds of olivine and chromite sand, the burn-on is much less. Unalloyed steel burns on rather strongly in olivine sand moulds, but its penetration is low. In the discussions that followed, the limitations

to the use of Indian olivine and chromite sands were discussed.

Dr D. Boenisch and Dr W. Patterson (West Germany) reported the results of studies on the effect of different types of coal dusts when used in foundry practice on the performance of the moulds. It has been found that finely pulverized coal dusts, which soften insufficiently or do not soften at all, increase the sand stresses developed by the casting heat, and thus promote the formation of scales and mould wall movement. The use of coals, which start softening early (below 400°C.) and have wide softening range, has been recommended; pitches have a particularly favourable effect. The new equipments developed at the Aachen Technical Institute, West Germany, for testing the performance of moulds were described. It was stressed that green and shear strength values no longer give a reliable estimate of the performance of moulds.

Mr D. Epstein (UK) gave useful details of the use of furfuryl alcohol binders in the production of intricate castings. These binders are new for Indian foundries. The discussion centred round the application, reclamation and reconditioning of the materials. Among the major conclusions emerging from detailed studies on moulds incorporating these binders are: (1) the speed of setting of a sand with these binders depends upon the maximum temperature reached; (2) the strength of the sand depends on the homogeneity of the binder film; (3) the water present and produced during the condensation process can separate and affect the bond by breaking continuity of the film of hardening resin with diminishing water tolerance and this is largely prevented by urea-formaldehyde resin; and (4) sulphonic acid being more soluble in these resins produce a stronger bond.

Mr V. Otàhal (Czechoslovakia) discussed the economics of production of grey iron castings in skin-dried moulds. In the study, operational data obtained from the leading Czechoslovak foundries making grey iron castings by this technique were used. A parabolic relation has been derived between the time and depth of mould drying, the drying temperature being constant. The rate of mould drying drops with increase in moisture content provided the drying temperature is constant. The type of moulding sand mixture and its permeability does not affect the intensity of mould drying. The intensity of drying is appreciably influenced by the direction and rate of the drying medium.

Dr J. Szreniawski (Poland) furnished results of investigations on hardness determination of foundry sand moulds using a conical indenter. It has been observed that the nature of variation of the hardness of moulding sands depends upon the loading force in the same manner as in the case of metals. As a result of this investigation, the method based on indenting of the mould cave surface by a conical indenter of 8 mm. diam. and with an apex angle of 120° under the action of 1000 *g* force, has been found to be the most convenient one for hardness determination.

Mr A. Evseev, Dr Aksjonov, Mr L. Baryshevski and Mr A Gorjatchev (USSR) described several automatic moulding lines in operation at a number of Soviet machine-building works. After stating the advantages of high pressure moulding with a solid squeeze block, using both normal and special high flowability moulding sand, the authors described four automatic lines equipped with both multi-station rotary type and single-station continuous type automatic moulding machine. The reliability of the lines was discussed with reference to their layout, e.g. lines with rigid connection and flexible lines with separate working stations and individual storage conveyors.

Dr A. M. Petrichenko (USSR) presented a paper on "Thin-walled permanent mould castings and thermal behaviour of permanent moulds". The paper, apart from furnishing data relating to thin-walled cast iron castings and the effect of thermal behaviour of the metallic moulds, also examined the dynamics of strain in the iron mould walls as a method of calculating the optimum thickness of the mould. Recommendations were made on the composition of the iron for moulds as well as the liquid metal properties to achieve stability of thin-walled castings.

Treatment of Liquid Metals

Four papers were discussed during this session. Dip. Ing. H. Mayer (Switzerland) presided.

Dr J. Duflot (France) dealt with the problem of deoxidation of steel, particularly C-O, C-Si-Mn-O and Al-O correlations. The problem of deoxidation, he stated, should not be treated merely from the thermodynamic point of view, but should also consider the mode of formation of deoxidation products and their elimination from the metal bath, the process of precipitation of inclusions during solidification, and the secondary reactions due to the use of special deoxidants.

Mr M. Decrop (France) pointed out that it was possible that crystallization of graphite in cast iron is linked with the appearance, though for a brief period, of silicon carbide, whose formation is caused by a local concentration of silicon. This inference gets support from the experimental observation that silicon carbide was visible only in high silicon cast irons (15 per cent) of homogeneous compositions. In cast irons of lower silicon content, silicon carbide appears only when heavy inoculations are made.

Dr F. Varga (Hungary) discussed the problem of development of eutectic cells and of graphite inclusions in industrial cast irons, and the influence of modification of the irons on the cells and inclusions. The number of eutectic cells has been observed to depend on the carbon content and, therefore, on the degree of saturation of the iron. The silicon content has no influence on the number of cells. The earlier results with regard to the effect of Mn, P and S contents could not be confirmed. The combined effect of variation in composition and modification, through overheating, is a substantial increase in strength. While the increase in strength with change in composition is accompanied by an increase in the number of cells, with modification the number falls.

Dr C. Pelhan (Yugoslavia) stated that the shape of graphite in cast grey iron depends mainly on the

number of nuclei and the composition of the melt. The effect of composition is reflected in the more or less marked tendency of cast iron towards graphitization. The higher the degree of saturation and the graphitization factor (K), the easier is the precipitation of graphite. He stressed that the larger the number of nuclei present in the melt, the sooner the onset of graphitization begins. Also, the lower the extent of sub-cooling, the coarser are the lamellae of graphite formed. The number of nuclei in a melt is influenced by the melting temperature, the cooling rate, inoculation and the purity of the melt.

Melting and Production Techniques

Ten papers were presented and discussed on the subject in two sessions held under the chairmanship of Mr M. M. Hallett (UK) and Dr A. Wittmoser (Germany).

Mr G. Greig (UK) speaking on modern ingot production said that for many years ingot moulds were manufactured in Great Britain by the 'dry sand' process utilizing natural clay-bonded sand. By using the recently developed cold setting synthetic sand process, not only the drying time and use of stones can be eliminated, but also the utilization of moulding boxes can be doubled. He further stated that the introduction of liningless basic hot blast cupolas, melting up to 100 per cent steel scrap, has resulted in a substantial reduction of melting costs in Britain where hematite pig iron costs twice as much as steel scrap. The life of the ingot mould made from hot blast cupola metal depends on the iron composition which can be controlled to produce excellent ingot moulds.

Dr C. Mitri and Dr R. Sacerdote (Italy) presented the results of studies undertaken to determine the optimum chemical composition of blast furnance iron for use in the production of ingot moulds for use in steel plants. Data on ingot mould life have helped in establishing the optimum percentages of silicon and manganese for ensuring a service life comparable to that of cupola iron moulds.

Mr J. E. Rehder (USA) described the current iron melting practice in North America and the trends of technological development covering the cupola in various modes of operation, the air furnace and the electric furnace. A new fuel-fired process for preheating electric furnace charges very rapidly to high temperature, which decreases both capital cost and power consumption, was outlined, and the application of gas producers to iron melting as an important practical fuel resource was examined.

Mr J. Drachmann (Sweden) dealt with the problem of blast velocity in the tuyeres and its influence on the working of liningless hot blast cupola. He presented a critical appraisal of the results reported on the subject from various research centres, in particular the laboratories of the British Cast Iron Research Association. Based on the material available in literature, the author endeavoured to present a complete picture of the melting process in a basic liningless hot blast cupola.

Dr U. K. Bhattacharya (India) discussed the experimental results of the investigations on the development of ferritic and pearlitic grades of black-heart malleable iron for the automobile industry. Experimental test bars cast from 100 lb. melts of base iron containing total carbon 2·40-2·55, silicon 1·40-1·55, manganese 0·35-0·45, sulphur 0·06-0·07, and phosphor 0·06 per cent (max.) were malleabilized in a muffle furnace under controlled conditions. The ferritic malleable iron obtained had good combination of mechanical properties and microstructure. The practice established in the laboratory was applied with some modification for production in the foundry for overcoming various problems encountered. The author also described the various tests employed to control the quality of castings.

Mr A Paucard (France) discussed the design, layout and main features of a foundry with a rated capacity of 70 metric tons/day and envisaged to produce 400 types of malleable iron parts and 200 types of cast steel parts set up at Lorient. The paper dealt particularly with the solutions for the problems encountered in respect of (1) general installation, (2) melting section, (3) standardization of methods for treating different products and (4) air-conditioning.

Prof. A. Balewsky and Prof. I. Dimov (Bulgaria) discussed the method of casting under counter pressure. The method of casting under counter pressure permits the control of all factors involved in the casting operation and thereby ensures flawless casting of uniform quality to be obtained. The choice of effective counter pressure on the mould during casting and crystallization permits (i) feeding of all thermal centres of the casting with comparatively small feeding heads acting under pressure and in which concentrated and well rounded off shrinkage cavities are formed; (ii) setting the infiltration pressure at the value required; (iii) plastic deformation of the growing crystallites at a temperature near the solidus in order to avoid the 'natural porosity' of the casting; and (iv) holding back in solution the gases contained eventually in the molten metal and thus avoiding the formation of micro and macro blow holes.

Dr B. R. Nijhawan, Mr J. Mohan, Mr J. Goswami and Dr A. B. Chatterjea (India) presented the results of pilot and industrial scale trials using substitute fuels like naturally burnt coke, low temperature carbonized coke from non-coking coals, carbonized lignite briquettes and coke-breeze blocks in cupola iron melting in order to conserve the limited reserves of metallurgical grade coking coal. Data on textural characteristics of the fuels tried, economics of their industrial scale utilization and availability were presented.

According to the authors, among the different varieties of non-metallurgical fuels, low temperature carbonized cokes were found to be fully satisfactory for substituting hard coke in the split charge except 'Kolsit' from Kothagudem, carbonized lignite briquettes and coke-breeze blocks. The coke-breeze blocks and carbonized lignite briquettes were totally unsatisfactory due to the disintegration under load at high temperatures. The low temperature carbonized cokes, such as those from Wardha Valley coal (Maharashtra) and Jhama coal with high shatter index showed better performance in the cupola

than those having low shatter index values and higher abrasion index, i.e. 'Kolsit' from Kothagudem. The substitution of the hard coke in the bed by any non-metallurgical fuel was impracticable due to its smaller size and presumably because of its high reactivity. The large particle size of the substitute fuel led to better melting performance. The composition of the molten metal, its temperature and fluidity were not significantly altered by the replacement of hard coke by the substitute fuels. The suitability of the substitute fuel recommended was conclusively demonstrated in industrial scale trials.

Mr R. C. Prosad, Drs S. S. Khanna, T. B. Singh and K. B. Mehta (India) described the different types of rolls for steel mills and dealt with the melting equipments used, their characteristics, effect of charge material and the manufacturing methods with chill control test. The authors also described the work carried out at the Foundry Forge Plant, Ranchi, on the manufacture of experimental rolls.

Mr B. L. Sen and Mr P. K. Bose (India) gave an account of the technological developments in foundry scale steelmaking with data obtained from trials carried on (1) improvements over the conventional electric furnace steelmaking using special oxy-fuel burners; (2) combined oxy-fuel burner/oxygen lancing technique for melting and refining to steel starting from cold scrap/pig iron in one and the same converter type vessel; (3) air/oxygen-enriched air basic side-blown converter technique for refining pig iron to steel of suitable foundry quality; (4) FOS process using 100 per cent steel scrap; (5) basic side-blown converter technique using submerged water-cooled oxygen lance; and (6) plasma-arc technique of making special quality steel. The authors have also made a comparative study of the various foundry scale steelmaking technologies to suit Indian raw material conditions.

The authors recommended that cold-charged electric furnace using oxy-fuel burner is suitable for medium to big foundry installation. The prospects of its immediate applications in the existing Indian arc furnaces as an aiding tool are bright. Cold-charged electric furnace following fuel-oxygen-scrap (FOS) process without electrical energy is suitable only for medium to big foundry installations. Its commercial application under Indian condition is yet to be studied. Cold-charged open-hearth furnace with mobile roof burner involves high capital investment and is not very suitable under the existing set-up of Indian foundries. Cold-charged basic lined converter with oxy-fuel burner is suitable for small-scale foundries with low capital investment, provided oxygen is available at reasonable rate. Its prospects under Indian conditions, particularly with small foundries dealing with quality castings, are bright. Air oxygen side-blown basic converter with proper melting units is attractive due to low capital investment and it is very suitable under conditions existing in India. Side-blown basic converter using submerged oxygen lancing technique has not been tried on bigger scale for commercial adoption and its suitability for application under Indian condition is yet to be studied. Plasma-arc melting technique is suitable for making special high vacuum quality steel and is not yet suitable for immediate adoption in India.

Factors Affecting the Mechanical Properties of Cast Irons and Alloy Steels

Five papers were presented at this session, presided over by Dr J. Van Eeghem (Belgium).

Mr Elisabeth Plenard and Mr Jöel Plessier (France) in their paper on "The elastic limit of cast iron — accommodation limit and role of time factor" discussed those characteristics of grey cast iron which have a bearing on their utilization. The authors attempted to replace the elastic limit of cast iron by another characteristic better adapted to the true behaviour of cast iron. Stress-strain relationship under tension has been studied and it has been found that two parameters, accommodation and time, could modify this relationship. Cast iron presents a very distinct accommodation phenomenon. It has been shown that below a maximum stress value, the cyclic repetition of the application of loads gradually leads to a stable and closed form of the cycle of the stress-strain curve; at the same time, residual strain gradually decreases and is finally eliminated after a certain number of cycles, which varies with the intensity of the maximum stress attained and the nature of the metal tested, which is the phenomenon of hysteretic accommodation. On exceeding the maximum stress, the shape of the stress-strain curve also becomes stable, but the residual strain is not eliminated and tends towards a constant value.

Mr K. Ono, Dr H. Tanimura, Dr K. Kodama and Mr K. Sato (Japan) discussed the effects of tramp elements on foundry pig iron. When different pig irons are subjected to nodularizing treatment with magnesium, the spheroidization of graphite is influenced by tramp elements, particularly Ti and As. To achieve good spheroidization, the total concentration of the tramp elements present should be less than 0·2 per cent. Tramp elements have also an important effect on the malleability of white cast iron. The total concentration of the undesirable elements, including S, V, As, Sn, Pb and Sb should, therefore, be kept very low to obtain white cast iron with satisfactory malleability.

Mr H. L. Roes and Mr W. Witte (Germany) presented the results of experiments carried out to determine the effect of wall thickness on the primary structure and the mechanical properties of plain carbon and alloy cast steels. It was established that ghost lines have little influence on mechanical properties. In addition to the pattern of the crystallization zone, the deterioration of purity of castings relative to freezing progression, in particular the weakening of the primary grain boundries, brought about by the precipitation of sulphides and carbide, should be regarded as a major cause.

Dr H. Siepmann and Dr F. W. Hauptvogel (Germany) discussed reasons for the differences in the mechanical properties of cast steel and hot-formed cast steel GS-30 CrMoV 6 4. Data obtained on various characteristics indicate that the differences do not

result from higher porosity of cast steel compared to the formed material. Grain size difference and degree of purity also seem to have no relation to the observed differences in mechanical properties. Possibly the increased toughness of forged steel is the result of elongation of the hard segregation zone.

Mr Res Küpfer (Switzerland) described a new grade of cast steel containing about 13 per cent chromium for hydraulic machinery. While possessing corrosion resistance to chloride solutions comparable to that of normal 13 per cent chrome cast steel, the new grade cast steel has other advantages, such as more favourable combination of strength and toughness properties, lower loss of impact strength with decreasing temperature; improved resistance to attack by sand erosion and cavitation, and better weldability. Thus, the maintenance costs on hydraulic machines are reduced with the use of this steel.

Alloying Additions and Their Effects on Properties of Cast Metals

Five papers were presented in this session held under the chairmanship of Dr M. Cenek (Czechoslovakia).

Mr G. G. Nair, Dr S. S. Bhatnagar, Mr P. K. Gupte and Dr B. R. Nijhawan (India) furnished results of researches carried out at the National Metallurgical Laboratory, Jamshedpur, on the effects of micro-addition of sulphur, sodium and phosphorus to aluminium-silicon eutectic alloy. It was found that micro-additions of sulphur effectively modify the alloys both in hypo- and hyper-eutectic ranges. A comparative study was made on the sodium-modified and sulphur-modified alloys in relation to their microstructure, mechanical properties and fluidity characteristics. Both the sulphur-modified and sodium-modified alloys possessed identical microstructure and mechanical properties, but differed in their fluidity patterns. Phosphorus was found to interfere with the modifying action of sodium in the eutectic alloy but not of sulphur.

The results of studies on the influence of Ag and Cd addition on the properties of aluminium cast alloys with 10 per cent Mg were furnished by Mr F. J. Kievtis and Mr A. J. Zuithoff (Netherlands). The effect of addition of Ag (up to 0·4 wt per cent) and Cd (up to 0·2 wt per cent) was investigated. The influence of Cd was less than that of Ag, but simultaneous addition of Cd and Ag increased the maximum hardness of the alloy, which is in agreement with the state of dispersion of the precipitate. Addition of Ag up to 0·1 per cent and Cd up to 0·5 per cent improved the mechanical properties of the 10 per cent Mg alloys; both tensile and yield strengths improved, but ductility was lowered.

Mr H. Mayer (Switzerland), in his paper entitled " Production of cast iron with improved strength and elongation by suitable charge materials and alloying additives ", stated that flake graphite formation on grey cast iron imparted a number of valuable characteristics to the cast iron, but impaired its mechanical properties, especially tensile strength and elongation. If alloying elements in suitable combination are added to a melt consisting of pure charge materials, it is possible to improve the tensile strength and elongation without major adverse effect on the favourable characteristics. He cited the example of a Ni-Cu-Mo-V alloyed cylinder liner for railway diesel engines, having tensile strength of 36·38 kg./mm.^{2} with a carbon content of 3·4 per cent at 200-230 kg./mm.^{2} Brinell hardness. A similar material with tensile strength 40 per cent better than that of unalloyed grey iron has been developed for cylinder covers.

Messrs V. I. Krestyanov, I. A. Vashookov, D. P. Ivanov and A. J. Kharapov (USSR) discussed some important methods of increasing the hardness and wear resistance of machine castings. Combined additions of boron and nickel to grey iron intended for casting large machine parts weighing up to 30 tons were found to be most effective for increasing the hardness and wear resistance of the castings.

Mr J. Dilewijns and Mr C. Defrancq (Belgium) discussed the influence of copper and nickel on the stable and metastable eutectic temperature of cast iron. Copper and nickel were found to raise appreciably the equilibrium temperature of the stable eutectic while they slightly lowered the metastable eutectic temperature of cast iron. Copper and nickel were found to raise appreciably the equilibrium temperature of the stable eutectic, while they slightly lowered the metastable eutectic equilibrium temperature. The results confirmed the graphitizing effect of both the elements.

Solidification and Structure of Cast Metals

The session was presided by Mr H. Rosenthal (USA) and three papers were presented.

Dr R. Kumar (India), in his paper on " Recent developments in the structure of metals in liquid state and their influence on founding properties ", attempted to elucidate the structure of molten metals and alloys based on the work done at the National Metallurgical Laboratory. The paper considered the distribution and nature of the cluster in the liquid state and showed that the clusters nucleate crystallization and that the destruction of the clusters renders the nucleation of the solid phase more difficult during solidification. It was also shown that the solidified metallographic structure can be correlated with the structure in the liquid state and the recognition of this fact by the foundry metallurgist may lead to a strong, powerful and fundamental tool in controlling the microstructure and properties of castings.

Dr K. Chijiiwa (Japan) furnished results of research on the behaviour of molten metal poured into a mould cavity, employing paraffin and metals of different colours. It was observed that the flow mechanism of the moten metal is related not only to the friction behaviour of the liquid and the wall surface of the mould cavity but also to the growth conditions of the solid that develop inwards from the mould wall.

Dr S. Ghosh (USA), in his paper on " Segregation zones in multiphase alloy-melts — A new foundry variable in 'still' and 'motion' castings ", contended that, during cooling of a multiphase alloy from its superheat temperature to the liquidus, there is a gradual transition of the phase-constituting atoms towards increased clustering (or ordering) so that

an optimum (for each set of conditions) dynamic pattern of their 'segregation zones' results in the liquid prior to solidification. It was proposed that the solidified structure is a product of transformation from this initial state of 'segregation zones' and, therefore, should bear the 'genetic' resemblance. The logical conclusion from these arguments, based upon direct and indirect evidence, was that the cast structure of such alloys may be readily influenced by controlled variations of the 'segregation zones' in the liquid prior to solidification.

U.N. Sessions

Specific problems of the foundry industry in the developing countries were discussed at a special session organized by the Centre for Industrial Development, United Nations. Eight papers were presented and discussed in two sessions presided over by Dr P. Schneider (W. Germany) and Mr L. B. Knight (USA).

The papers discussed included: Growth pattern of foundry industry in developing countries (Dr B. R. Nijhawan); Planning of heavy foundry (Dr B. D. Kalelkar); Investment casting (Mr H. Rosenthal); Precision casting of special alloys (Dr D. F. B. Tedds); Mechanization and plant layout (Dr O. J. Holownia); Liquid metals (Dr M. Maurakh); Secondary alloy castings (Dr C. Mascre and Dr D. Arnaud); and Progress in cast iron smelting (Prof. L. M. Marienbach).

Dr Nijhawan pointed out that the developing countries have to choose and accept not necessarily the best and the latest available technology, but the one suitable to their overall pattern of industrial growth, economic stature, market trends and consumer needs. He cited the example of the development of the foundry industry in India and the role of research in foundry technology.

Dr B. D. Kalelkar described the way the heavy foundry at the Heavy Engineering Corporation, Ranchi, was planned and installed. He opined that the establishment of such modern foundries would have great impact on the development of the engineering industries in the ECAFE region.

Discussing the role of investment casting, Mr H. Rosenthal highlighted the critical character of the economic factors influencing the successful application of the process. The economic determinants of shell moulds versus solid moulds were likewise considered. He emphasized that the choice of a casting technique depended on the number of castings required because of its direct influence on amortization of die costs. Continuing the trend of discussion started by Mr Rosenthal, Dr D. F. B. Tedds said that the development of the gas turbine engine and the requirements of aerospace industries had given a great impetus to stimulate advances in the technology of precision investment casting. He described the special furnaces, crucibles, vacuum melting techniques, and other parameters of special alloy castings. The quality requirements of the alloy stock used for re-melting and forming investment casting were also spelt out.

Mechanization and plant layout of steel and non-ferrous alloy foundries was discussed by Dr O. J. Holownia. The range of application of the right machinery and equipment was illustrated by a foundry production flow diagram. He pointed out that while mechanization of foundries, where the number of castings required was large as in the automobile industry, had proceeded well, less work had been done on plant layout problems of foundries turning out single castings or small lots of castings.

Dr M. Maurakh discussed liquid metals and presented comprehensive data on the properties of iron, titanium and zirconium in the liquid state. He also discussed the improvements in the theories of spreading liquid reactive metals on the surface of a solid material and its penetration into a porous solid body.

In the developing countries the recovery of metals through melting scrap is very important. The recovery industry is both the customer and the supplier for metallurgical industries. Dr C. Mascre and Dr D. Arnaud discussed these aspects with special reference to the production and treatment of secondary alloy castings. They stressed that secondary alloys were not as pure as those obtained from ores. Therefore, the processes adopted in secondary smelting should avoid all contamination. They emphasized the need for standardization in order to reduce the number of grades, and thereby the weight of stocks.

Progress in cast iron smelting was discussed by Prof. L. M. Marienbach. He dealt with the reduction in the cost and improvement in quality of molten cast iron. According to him, cast iron could be obtained at a lower cost by reducing the consumption of pig iron through increased use of scrap and self-recovery products. In the countries possessing natural gas deposits, cost reduction could be achieved through a complete or partial replacement of coke by gas. He also pleaded for maximum possible mechanization and automation of casting equipment. He pointed out that despite such good prospects for the electric smelting of cast iron, the conventional cupola would remain the major source of cast iron for many years to come. The latest improvements in cupola melting had made it possible to obtain quality metal of specified chemical composition, and softening behaviour, using comparatively low-cost charges.

Concluding Session

Mr W. E. Huber, President of the Congress, said at the concluding session, "The 33rd International Foundry Congress is of exceptional importance to the development of our Committee because the fact that it is being held in India is a proof that the foundry industry is prepared to promote technical progress through generous international exchange of technical ideas and experience, and furthermore to make a valuable contribution to the industrialization of aspiring nations". Mr Huber pointed out that apart from metallurgical problems and the endeavour to increase productivity, attention should be devoted to the fundamental questions of metal casting.

He announced venues for next few annual sessions of the IFC as agreed by the Executive Committee of the CIATF: 1967 (France), 1968 (Japan), 1969 (Yugoslavia), 1970 (Britain), 1971 (West Germany), and 1972 (USA).

Dr F. Singut (Austria) and Mr S. Holmblad (Denmark) were elected President and Vice-President respectively of the 34th Congress. Representatives of the member associations on the CIATF were: Prof. M. B. Pajevic (Yugoslavia), Dr C. Pensotti (Italy) and Dr H. Friederiches (West Germany). Representatives of the Past President's Council were: Dr A. B. Everest (Britain), Mr J. M. Boucher (France) and Mr W. E. Huber (Switzerland). The Executive Committee of the CIATF appointed Mr W. E. Huber as the representative of the Past President's Council. Dr H. Hoffmann (Switzerland) and Mr Fauquembergue (France) were appointed Presidents of International Commissions on 'Moulding Materials and Refractories' and 'Technical Progress' respectively.

Foundry Book Exhibition

During the congress, the Indian National Scientific Documentation Centre (INSDOC) and the Institute of Indian Foundrymen jointly organized an exhibition of books and periodicals on foundry technology at Vigyan Bhavan. A catalogue, listing the exhibits, covering about 580 titles published in 18 languages received from 20 countries was brought out. "Bibliography on Foundry Practice" and "Foundry Directory of India" — the first of their kind — were brought out by the INSDOC and the Indian Institute of Foundrymen on the occasion. The exhibition also displayed photographs of castings and actual intricate cast models.

Awards

Mr W. E. Huber, President of the 33rd International Foundry Congress, was awarded a silver plaque by the Indian Institute of Foundrymen for his outstanding contribution to the development of foundry industry. Dr B. R. Nijhawan, President of the Indian Institute of Foundrymen, received a silver plaque in recognition of his service to the progress and development of foundry industry in India. Mr Arjan Vaswani and Mr R. M. Krishnan received gold medals in recognition of their valuable contributions in the field of foundry technology and industry, and for their meritorious services for organizing the congress.

Ground & Lake Water Resources in India — A Symposium

A symposium on ground and lake water resources in India will be held in December 1967 at Hyderabad. Organized jointly by the Indian Geophysical Union and the National Institute of Sciences of India, the symposium will be devoted to studies in hydrology of lakes, reservoirs and underground water in the country.

During the symposium it is proposed to reassess the water resources in the various regions of the country and thoroughly examine the problems of development and utilization of these resources. A steering committee has been set up with Dr S. Bhagavantam (Convener), Dr K. R. Ramanathan, Dr M. S. Krishnan, Dr G. C. Chatterjee and Dr S. Balakrishna as members to plan and organize the symposium.

Intending participants should send 500-word abstracts of papers to reach the Secretary, Indian Geophysical Union, Hyderabad, not later than 1 October 1967. The full texts of papers with diagrams drawn in Indian ink on Bristol board or tracing paper should reach the Secretary by 1 December 1967.

Optical Centres in Alkali Halides: Part II — Z Centres*

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DETAILED work on electrical conductivity, diffusion and density changes in alkali halides, done by earlier authors and reviewed by Lidiard[1], shows that alkaline earth impurities go in the alkali halide lattice as substitutional impurities in the M^{2+} state where M stands for calcium, strontium or barium. Since the divalent impurity ion has an extra positive charge and the cation vacancy, created by the impurity to keep the crystal electrically neutral, carries a negative charge, they interact with each other with long-range Coulombic forces. The energy of association of the divalent impurity and the vacancy pair is of the order of 0·3 eV. and at room temperature almost all the impurities and the vacancies created by them would be associated to form the impurity vacancy pairs.

The optical absorption in alkali halides doped with alkaline earth impurities has been a subject of great interest ever since Pick[2] first studied them in 1939. The alkaline earth impurities — calcium, strontium and barium — introduce significant changes in the optical absorption of additively coloured or irradiated alkali halide crystals. Five new bands are now known[3] to be associated[2,3] with these impurities and are called the Z_1, Z_2, Z_3, Z_4 and Z_5 bands. The models for the centres responsible for the first three bands were first suggested by Pick in 1939 but were later altered by Seitz[4] in 1951 who gave new models for these centres with considerable support from experimental data existing at that time. These models have, however, been a subject of great controversy during recent years and a variety of experiments involving dichroism, dielectric loss, conductivity, electron power magnetic resonance (EPR) and electron nuclear double resonance (ENDOR) have been performed seeking confirmation of one or the other of the two sets of models. In the process, however, need was felt for entirely new models and four major approaches are now known. The earliest ones due to Pick and Seitz were followed by those due to Kleefstra[5] and Hartel and Luty[6], based on optical and thermal studies of Z centres and of Ohkura[7] arrived at by the use of EPR. Considerable advances in our understanding of these centres have been made by ENDOR measurements performed recently by Bushnell[8] and dielectric loss measurements by Bucci *et al.*[9]. We propose to give a connected account of the various investigations and a critical review of the present state of our understanding of the nature of the Z centres.

Early Work on Z Centres

It is found that if an additively coloured crystal, which contains the pure F band, is bleached by the F light, new centres, termed Z_1, associated with alkaline earth impurities are obtained. When such crystals are heated to about 110°C., the Z_1 band vanishes and a new band called the Z_2 band develops, and this Z_2 band is completely destroyed on raising the temperature to 200°C. If, however, the bleaching with F light is done at −90°C., both the F and Z_2 centres diminish, and two new bands — the F' and Z_3 — are observed. Prolonged irradiation with F light, however, produces a new band termed Z_4. The peak positions, half-widths and oscillator strengths of some of the Z bands are given in Table 1. Typical absorption under some of the Z bands in KCl is shown in Figs. 1 and 2.

Fig. 3 gives the various models for the Z centres suggested by different authors. According to Seitz's model the Z_1 centre is an isolated divalent ion which has captured an electron. The essential difference between the models proposed by Seitz and Pick for the Z_1 centre is that whereas the vacancy remains an integral part of the centre in Pick's model it is removed from the centre in Seitz's model. Apparently, Seitz found it necessary to exclude the cation vacancy from the model for the Z_1 centre, since the central field will not provide enough binding energy for both the electron and the cation vacancy to enable the Z_1 centre to be stable at room temperature. A close similarity of transformation of F to F' centres and Z_2 to Z_3 centres observed by Pick led Seitz to believe, in agreement with Pick, that the Z_3 centre is a Z_2 centre which has captured another electron. It was emphasized that in the case of F' centre the field is central whereas in the case of Z_3 centre, proposed by Seitz, the two electrons made use of the attractive field of both the halogen ion vacancy and the divalent ion, and in view of this the occurrence of Z_3 band towards the shorter wavelength side of the Z_2 band is not surprising. Seitz was able to show that the formation of Z_2 centres above 110°C., incomplete F to Z_1 conversion, high optical stability of Z_1 centres and other characteristics of the Z bands were consistent with his models.

Seitz also suggested critical experiments to check on the models he had proposed. He suggested that Z_2 centres should be formed if additively coloured crystals are slowly cooled and that R and M bands must be formed during the optical conversion of F to Z_1.

Further Experiments on Z Centres

After Seitz's long paper re-interpreting the experiments of Pick on the Z bands, a large number of experimental physicists in the United States, Europe and Japan devised experiments to study the detailed behaviour of the Z bands and to check whether the behaviour agreed with the predictions based on Seitz's model. The early work was done by the Italians. The main results of this work supported Seitz's models. Camagni and Chiarotti[10] found

*Paper presented at the convention organized by the Physical Research Committee of the Council of Scientific & Industrial Research at the Banaras Hindu University, Varanasi, in March 1967.

TABLE 1

		Z_1			Z_2		Z_3		Z_4	
		Peak position eV.	Half-width eV.	Oscillator strength	Peak position eV.	Half-width eV.	Peak position eV.	Half-width eV.	Peak position eV.	Half-width eV.
KCl	Ca	2·10 (ref. 11)			2·07	0·28	2·53			
	Sr	2·00 (ref. 11)	0·46 (ref. 10)	0·84 (ref. 10) 0·90 (ref. 5)	1·95	0·26	2·50		1·48 (ref. 21)	
	Ba	2·06 (ref. 11)			1·94 1·52	0·35 0·18				
KBr	Ca				1·77	0·32	2·23			
	Sr				1·73	0·32	2·22			
	Ba				1·73 1·46	0·45 0·20				
NaCl	Ca				2·63	0·30	3·10			
	Sr	2·45 (ref. 11)			2·44	0·20	3·10			
	Ba									

Values other than those for which the authority is cited are taken from ref. 3 [K. Kojima, *J. phys. Soc. Japan*, **19** (1964), 868].

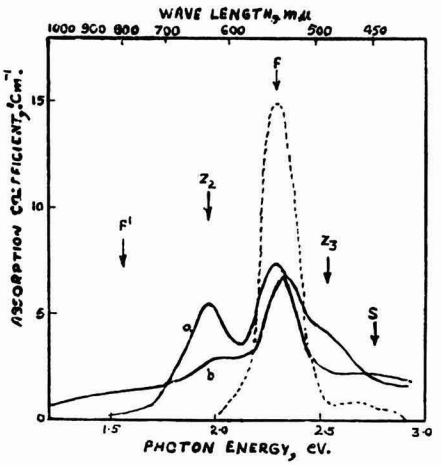

Fig. 1 — Optical absorption of a KCl: Sr crystal at 78°K. [Dashed curve is obtained after additive colouration. Curve a: Absorption after optical bleaching of the F band and formation of the Z_2 and S bands. Curve b: Absorption after optical bleaching of the Z_2 band and formation of the Z_3 and F' bands. After H. Ohkura, *Phys. Rev.*, **136** (1964), 446]

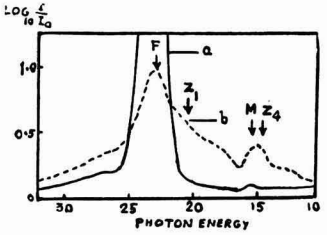

Fig. 2 — Optical absorption of a KCl: Sr crystal (a) before F light irradiation and (b) after F light irradiation, showing the positions of Z_1 and Z_4 bands [After M. Ishiguro & N. Takeuchi, *J. phys. Soc. Japan*, **15** (1960), 1871]

that Z_2 centres could also be formed directly from the F centres by warming the doped coloured crystals in dark. A value 0·84 was obtained for the oscillator strength of Z_1 centre in KCl: Sr using Smakula's formula. If modified Smakula-Dexter formula is used, the value will change[11]. We have used the old values since the values based on Smakula's formula have been extensively used in literature. The oscillator strength appears to be very close to that of the F centre which is 0·81 eV. and this is to be expected in view of the similarity between the F and the Z_1 centres. They have also determined the half-widths of the Z_1 band in KCl: Sr and this value is included in Table 1. They obtained Z_1 concentration by bleaching the additively coloured crystals with F light. They found that only a part of the impurity was effective in producing the Z_1 centre. Knowing the total amount of impurity present in the crystal and also the impurity in the isolated state and applying the law of mass action they were able to evaluate the energy of association of the impurity with a positive ion vacancy. The value 0·3 eV. for the energy of association obtained in this manner is in reasonable agreement with the value of energy of association derived for divalent impurities from conductivity and diffusion data. Camagni and Chiarotti[10] were also able to determine the number of negative ion vacancies initially present in the crystal. They obtained a value of the order of $1{\cdot}4\times10^{17}$ cm.$^{-3}$. Though there was no alternative measurement of the negative ion vacancy concentration in 1954 when Camagni and Chiarotti published their paper, the negative ion vacancy concentration has recently been determined by the F centre growth rate[12] measurements and by the thermoluminescence[13] measurements. The value of the negative ion vacancy concentration determined in these papers is $\sim 10^{18}$ cm.$^{-3}$ and is in fair agreement with the value $1{\cdot}4\times10^{17}$ cm.$^{-3}$ obtained by Camagni and Chiarotti.

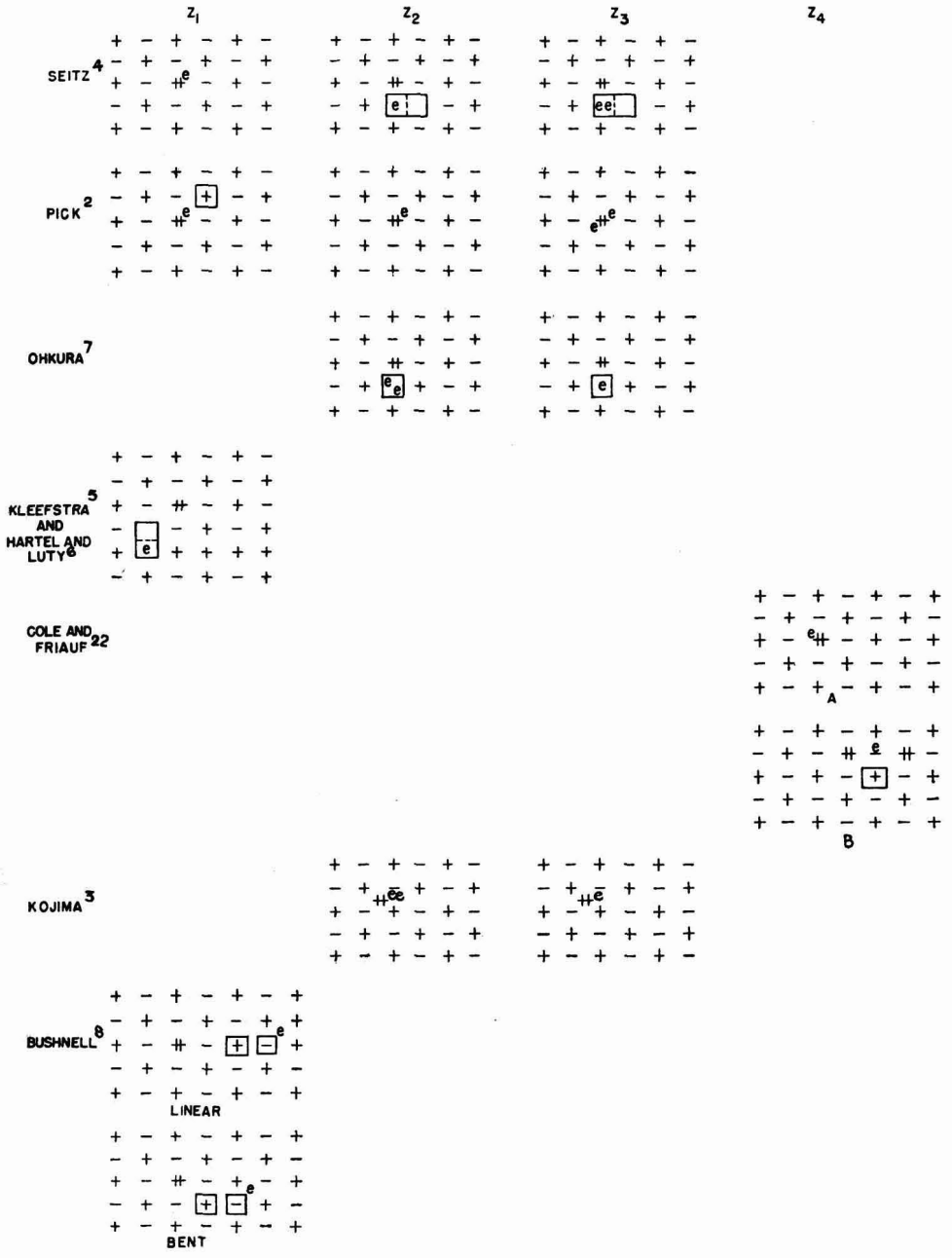

Fig. 3 — Various models proposed for the different Z centres

Seitz had suggested that conversion of Z_1 centre to Z_3 centre is by the migration of the fast-moving vacancy-vacancy pair to the Z_1 site. It is now known from the work of Tharmalingam and Lidiard[14] that this pair does not move so fast. In fact, the energy needed for the migration of this pair is slightly more than the energy needed for the migration of the positive ion vacancy. However, it is still possible to retain Seitz's model if we assume that either the F centre or the impurity vacancy pair moves which brings the impurity vacancy pair and the F centre together to form the Z_2 centre.

Recent Work on Z Centres

According to the models suggested by Seitz and Pick, both Z_1 and Z_2 centres have a paramagnetic single electron associated with them and, therefore, it should be possible to study these centres with the help of EPR and ENDOR techniques. The first paper on such studies was given by Kawamura and Ishiwatari[15] in 1958. These authors found that the EPR absorption line associated with Z_1 centres in KCl and NaCl has the same g value as that of the F centres but is somewhat broader with a half-width of 79 gauss. The line shape is Gaussian for both the F and Z_1 centres. According to Pick's model of the Z_1 centre it is an electron trapped with a divalent ion and associated with a positive ion vacancy. If this were to be correct, then the bound electron will find a preferential location away from the vacancy and the EPR line is likely to be triangular in shape. The fact that the signal was Gaussian in shape supports Seitz's model.

Conclin and Friauf[16] made a more elaborate study of the Z and F centres by EPR. The results of these authors agree with those of the Japanese as far as the g value is concerned, but they found that the half-width of the line due to Z_1 centre was 63 gauss. Conclin and Friauf have found that Z_2 centres are also paramagnetic and have pointed out that the discrepancy between their results and those of Kawamura and Ishiwatari[15] may be due to the fact that there were some Z_2 centres involved in the experiments of Kawamura and Ishiwatari. Though these results confirm paramagnetic nature of the Z_1 centre, it is not possible to make a conclusive choice between the Pick's and Seitz's models.

Ohkura[7] has made a thorough study of Z_2 and Z_3 centres by EPR and has found that Z_2 centre is not paramagnetic. He came to the conclusion that the Z_3 centre is a Z_2 centre which has lost one electron, and hence the Z_2 centre must possess at least two trapped electrons. This is in accordance with earlier observations of Ohkura and Murase[17] and those of Takeuchi and coworkers[18] who found that the Z_2 centre is diamagnetic. Ohkura also observes two new bands one due to the excited levels of Z_3 centre and the origin of the other, designated as S band, is similar to that of the α band. This is an exciton absorption band in the neighbourhood of the Z_3 centre. Ohkura and Murase find a half-width of 39 gauss for the EPR line due to the Z_3 centres which is much smaller than 58 gauss for the F centres. Based on these facts, Ohkura suggested new models for the Z_2 and Z_3 centres as shown in Fig. 3.

Another important contribution to the study of the Z centre has been made by Kojima[3]. She has determined the peak positions, half-widths and other parameters of the Z_2 and Z_3 bands (Table 1). She has also determined the Z_2 absorption peak as a function of the atomic mass of the divalent ions, the lattice spacing of the host crystal and temperature. She found that the peak shifts towards longer wavelength with increase of mass of the impurity ion and lattice spacing but is relatively insensitive to temperature. She has succeeded in drawing a configuration-coordinate diagram of the Z_2 centre. Based on her experimental results she found need to suggest independent models for the Z centres. In view of the fact that Z_3 centres are formed only when Z_2 and F centres coexist by Z_2 light at low temperatures where F' centres are stable and not when only Z_2 centres are present, makes her suggest that the F centres are the only possible traps for electrons released from Z_2 centres and a Z_2 centre cannot trap another electron. She also reports that in barium-doped crystals the Z_2 centre shows two absorption peaks. She proposes a neutral alkaline earth atom located at an interstitial site as a possible model for the Z_2 centre. The alkaline earth atom is tetrahedrally surrounded by four halide ions and four alkali ions and the crystalline field prevalent is of tetrahedral symmetry. It can be shown by theoretical arguments that the tetrahedral crystalline field is not suitable to lift the 3-fold degeneracy of the p orbitals. The peak wavelength of the Z_2 band is temperature insensitive because thermal lattice expansion will have little influence on the energy levels of the interstitial atom. She has pointed out that the other possible models satisfying the same symmetry conditions do not satisfy the experimental facts.

Chiarotti *et al.*[19], Ishiguro *et al.*[20] and Ishiguro and Takeuchi[21] have studied the dichroic properties of Z centres. Chiarotti *et al.* could not detect any dichroism in Z_2 band. Ishiguro *et al.*[20] found that Z_1 centre has high symmetry and was not dichroic. They, however, found dichroism associated with the Z_2 centre when irradiated with $<010>$ polarized light. The dichroic measurements, therefore, support Seitz's models since Pick's model for Z_1 centre should show dichroism if bleached with light. Ishiguro and Takeuchi studied the dichroism of the Z_4 bands and have confirmed that the symmetry axis is in the $<110>$ direction as was expected from Cole and Friauf's model[22]. They have established that 'A' model (Fig. 2) of Cole and Friauf for Z_4 centre is justified since according to the 'B' model Z_4 centre is aligned along the $<100>$ direction (Fig. 3).

Lidiard[23] showed, by rigorous thermodynamic arguments, that the Z_1 centre of Seitz is very unlikely to obtain in any alkali halide crystals doped with alkaline earth impurities. Since in crystals quenched from 400°C. in the dark, the number of Z centres is negligible, the energy of ionization of Z centres should be much smaller as compared to that for F centres so that at 400°C. no Z centres are present in the crystal. This would

mean that the optical position of the absorption band due to Z_1 centre must be at about 0·8 eV. as compared to the observed position of about 2 eV. On the other hand, Johnson and Scott[24] have calculated the Z energy levels based on the Seitz's models of Z_1 centre and have found that the absorption band due to Seitz's Z_1 centre must lie at 8·0 or 9·0 eV. Though the accuracy of Simpson's method used in these calculations is not high, it has been highly successful in predicting the energy levels of the F centre and it is reasonable to assume that the values given for the Z_1 centre should at least be correct as far as the order of magnitude is concerned. This would again indicate that none of the Z absorption bands can be due to Seitz's model of Z_1 centre. Johnson and Scott have pointed out that it is possible that the absorption due to Seitz's Z_1 centres might have escaped notice because the absorption may lie in the far ultraviolet region. Peterson and Patterson[25] came closest to explaining the Z band positions by obtaining 3·14 and 2·59 eV. for Z_1 band position for Seitz's and Pick's model respectively.

Kleefstra[5] made detailed studies of the optical transformation from F to Z centres and suggested that the Z_1 centre is a complex centre involving vacancy pairs. He also estimated the oscillator strength of the Z_1 band as $0{\cdot}9 \pm 0{\cdot}2$ eV. The model proposed by Kleefstra was later suggested independently by Hartel and Luty[6], and essentially consists of a combination of an F centre with a complex of a doubly charged alkaline earth ion and a cation vacancy.

Bushnell[8] studied the ENDOR of calcium- and strontium-doped crystals. Seitz's model of the Z_1 centre is expected to give a resolved hyperfine structure in crystals doped with strontium which is enriched with the magnetic isotope ^{87}Sr. This was, however, not observed by Bushnell and he, therefore, concludes that Seitz's model is incorrect. He also did not detect any ENDOR absorption due to Z_2 centres which in confirmation with earlier EPR work confirms the diamagnetism of the Z_2 centre. He has pointed out that the Seitz's model of Z_1 centre should give rise to a half-width of well over 100 gauss of EPR line while the observed half-width is only 63 gauss. Based on his observations he proposes two similar structures both present in calcium- and strontium-doped crystals but in different concentrations. One of these structures is similar to that proposed by Hartel and Luty as is shown in Fig. 3. This is called the bent model. The other model is called the linear model and is also shown in Fig. 3.

The key problem in deciding the validity of the model proposed by Kleefstra[5], Hartel and Luty[6] and by Bushnell[8] is to find whether or not the concentration of the impurity vacancy pairs decreases during the formation of Z_1 centres. Recently, critical experiments have been performed by Bucci *et al.*[9] to test whether the concentration of the impurity vacancy pairs decreases when the Z_2 centres are formed by exposure of the crystals to light. They found that the dielectric loss was not affected immediately on instantaneous conversion of F centres into Z centres by exposure of crystals to intense light. The dielectric loss decrease follows the conversion with a time lag. Bucci's work rules out the direct participation of the impurity vacancy pairs in the formation of Z_1 centres and does not support the models proposed by Kleefstra[5], Hartel and Luty[6] and Bushnell[8].

The major difficulty in the EPR and other studies of the Z centres in crystals containing alkaline earth impurities arises from the fact that F centres overlap the absorption due to Z centres and it is not possible to have a large number of Z centres without creating a comparable concentration of F centres. It seems that the studies of similar centres with other impurities of the group 2 elements might help resolve the problem connected with the nature of Z centres. Such measurements with zinc and cadmium impurities in alkali halides have been made by us recently (Jain, S. C. & Radhakrishna, S., unpublished data) and will be discussed in a separate publication.

Summary

Optical absorption bands due to alkaline earth impurities in alkali halides have been extensively studied. Though the absorption bands due to these impurities were discovered in 1939, extensive experimental work was done only during the period 1952-58. More definitive experiments have been performed during the last six or seven years after the new experimental techniques like EPR and ENDOR could be applied to the study of these centres. Dielectric loss, dichroic properties and many other physical properties of these centres have also been studied. The experimental and theoretical work on these centres, called the Z centres, is reviewed, and the relative merits of the various models proposed for the centres are discussed. Some further experiments which should be performed on these bands to make the nature of the models more clear are also suggested.

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Leghaemoglobin & Its Role in Symbiotic Nitrogen Fixation

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AMONG the several families of the plant kingdom, the family Leguminosae contributes a good deal to the nitrogen economy of nature through symbiotic association with the bacteria of the genus *Rhizobium* in nodules formed on the root system[1].

The core of a mature nodule constitutes the 'bacteroid zone' surrounded by several layers of cortical cells. The bacteroid zone is made up of host cells which contain enlarged, vacuolated and sometimes branched forms of *Rhizobium* called 'bacteroids'. A red pigment, leghaemoglobin, accumulates around the bacteroids in membranous envelopes. The bacteroids and the leghaemoglobin surrounding them are concerned with the intimate biochemical reactions involved in the process of symbiotic nitrogen fixation in the nodules.

Physico-chemical Properties

Exhaustive monographs[2,3] published in the earlier part of this century do not make any reference to the presence of a pigment in the root nodules. However, Pietz[19] appears to be the first to mention the presence of the red pigment in nodules and carry out a systematic study on the root nodules of *Vicia faba*. He considered the pigment to be identical with the red intermediate product, 5,6-quinone-2,3-dihydroindole-2-carboxylic acid, formed during the oxidation of tyrosine or dihydroxyphenylalanine catalysed by tyrosinase. It was postulated that the red pigment plays an important role in the oxidation-reduction potential facilitating bacterial proliferation. Later investigations showed the haemoprotein nature of the compound and its function as an oxygen carrier[4-6]. Several studies show that effective nodules always contain leghaemoglobin and the amount of the pigment in them is directly related to the amount of nitrogen fixed by the legumes[7-17].

The haemoglobin in root nodules has been referred to as 'leghaemoglobin' or 'legoglobin', the prefix 'leg' indicating its presence in legume root nodules[18]. However, some workers still prefer to call this nodule pigment as haemoglobin by virtue of its similarity with blood haemoglobin. The leghaemoglobin is a haemoprotein consisting of a haeme moiety attached to a peptide chain which represents the globin part of the molecule. Based on colour, three types of nodules have been met with in legumes — the pink, the green and the brown ones. All these types possess haemoglobin, but they are present in nodules in different states with reference to the haeme moiety. The pink nodules possess leghaemoglobin, while the green and the brown ones have 'legcholeglobin' and 'legmethaemoglobin' respectively. Leghaemoglobin is active in nitrogen fixation while the other two are relatively inactive[18]. Virtanen and Laine[18] suggested a scheme outlining the interconversion of the three types of pigments.

For a long time, haemoglobin was considered to be the prerogative of the animal kingdom until Pietz[19] reported the presence of a red pigment in root nodules of legumes which was akin to the haemoglobin of animal blood[4]. The similarity between the animal haemoglobin and the legume haemoglobin was shown by their similar absorption maxima[20-22]. The molecular weight of the legume haemoglobin is of the order of 16000-17000 (ref. 23-25) while that of blood haemoglobin is of the order of 66000. This variation is mainly because of the difference in the number of peptide chains between the animal and legume haemoglobins. The former contains four peptide chains each linked with one haeme moiety while the latter has only one chain linked with one haeme moiety.

Our knowledge concerning the physico-chemical properties and electrophoretic behaviour of leghaemoglobin comes from the work of Ellfolk and co-workers[23,24,26-33]. Leghaemoglobin from soybean nodules consists of two distinct components of different electrophoretic mobilities having isoelectric points at *p*H 4·4 and 4·7. The faster moving component has twice the haemin content of the slower moving component. The molecular weight of the faster and the slower components are 16800 and 15400 respectively on the basis of sedimentation constants, although the values are 16695 and 15429 on the basis of amino acid composition. The haemin of the two electrophoretic components has been found to be protohaemin; the iron content of the faster component is 0·32 per cent while that of the slower one is 0·28 per cent. The peptide chains of the two electrophoretic components are different as revealed by chromatographic patterns of their tryptic digests. The faster component contains a peptide chain with N-terminal glycine while the slower one has a chain with N-terminal valine, precluding the possibilities of

one component acting as a precursor of the other. Significant quantitative differences have been found between the two electrophoretic fractions with regard to alanine, glutamine, glycine, valine and isoleucine. No S-S bond has been detected in the molecule indicating the absence of cysteine and cystine.

Role of Leghaemoglobin

Three possible roles could be ascribed to leghaemoglobin in the process of symbiotic nitrogen fixation: (1) it participates in the early stages of nitrogen fixation through its trivalent iron atom which oxidizes the nitrogen molecule, e.g. $Fe^{3+}+N_2 \rightarrow Fe^{2+}+N_2O$; (2) it acts as an oxygen carrier; and (3) it forms a metallo-enzyme-nitrogen complex.

The first possibility rests on the hypothesis that Fe^{2+} changes to Fe^{3+} and then acts as an electron acceptor in accordance with the following scheme[18]:

N_2 + methaemoglobin (Fe^{3+}) = NH_2OH + haemoglobin (Fe^{2+})

↓ Oxaloacetic acid

1-aspartic acid ← oxime

Substantial support in favour of this hypothesis has not been forthcoming from other workers who did not observe any trivalent atoms in leghaemoglobin[4,10].

The second possibility becomes significant if nitrogen fixation is taken as a respiratory process during which nitrogen substitutes oxygen as an oxidant and acts as a terminal hydrogen acceptor[34,35]. Leghaemoglobin might act as an oxidation-reduction catalyst in symbiotic nitrogen fixation by functioning as an oxygen carrier[36-40]. Bergersen[41] put forth a hypothesis indicating the role of bacteroids and leghaemoglobin in nitrogen fixation. He also considers the pigment as an oxidation-reduction catalyst. The primary reaction is the activation of molecular nitrogen and its reduction to ammonia. The activated nitrogen is the ultimate acceptor in an electron transport chain which begins in the bacteroids. One of the links in this chain is leghaemoglobin. Carbon substrates supplied by the host plant are partially oxidized by the bacteroids and supply electrons for the reduction of the activated nitrogen. The incompletely oxidized substrates serve as acceptors of ammonia in the production of amino acids which diffuse away into the host plant. On the contrary, Yocum's failure[42] to detect any change in the ratio of Fe^{3+} to Fe^{2+} in nodule sections by changing the gas mixtures from those optimal for nitrogen fixation to those for zero fixation is a possible evidence against the hypothesis that leghaemoglobin operates as an oxidation-reduction catalyst.

The third possibility deals with the intermediate products formed in the conversion of nitrogen to ammonia. While it has been generally agreed that ammonia is a detectable key intermediate so far known in biological nitrogen fixation, little has been known regarding the intermediate products formed in the conversion of nitrogen to ammonia. In suggesting a mechanism for biological fixation of nitrogen with hydrazine as an intermediate, it has been postulated that nitrogen would react with an enzyme carrying two metal groups which bind the nitrogen during the initial reduction process to form a metallo-enzyme-nitrogen complex. This complex undergoes a cleavage to yield hydrazine and the free enzyme[43,44]. Studies with ^{15}N-labelled hydrazine[45] do not lend support to the concept of hydrazine acting as an intermediate since the isotope did not find its way to glutamic acid, an end product of biological nitrogen fixation. However, the possibility of hydroxylamine as an intermediate between nitrogen and ammonia has not been successfully verified because the compound happens to be unstable in dilute solutions.

The central portion of the haeme moiety of leghaemoglobin is the iron atom. The exposure of the haeme group to allow reactions with the iron atom is one of the key factors governing the participation of leghaemoglobin in nitrogen fixing process. It has been observed that the haeme group in leghaemoglobin is not normally located in an exposed position on the surface of the globin, but gets subsequently exposed during auto-oxidation in air when the haeme undergoes an irreversible rearrangement[46,47]. The first stage of nitrogen fixation would start with the adsorption of nitrogen to leghaemoglobin. This adsorption takes place at the haeme portion of the molecule which may occur in hydrated, oxygenated or hydroperoxyle states. The resulting product may be a labile leghaemoglobin-nitrogen complex. Simultaneously, hydrogen atoms are released by the adsorption of aqueous hydrogen to leghaemoglobin. These hydrogen atoms combine with leghaemoglobin-nitrogen complex to form a leghaemoglobin-nitrogen-hydrogen complex having a free radical $\cdot N_2H$. The latter complex would react with more of hydrogen atoms to form hydrazine and release leghaemoglobin. The hydrazine is further reduced to ammonia by the mediation of an enzyme, hydrazine reductase, a molybdoflavoprotein. The reactions could be summarized as follows[48,49]:

(i) Leghaemoglobin + N_2 → Leghaemoglobin-nitrogen complex

Leghaemoglobin + H^+ aq. → Leghaemoglobin (oxidized form) + $H\cdot$

(ii) Leghaemoglobin-nitrogen complex + $H\cdot$ = Leghaemoglobin-nitrogen-hydrogen complex

(iii) Leghaemoglobin-nitrogen-hydrogen complex + 3H = Leghaemoglobin + hydrazine

(iv) Hydrazine + 2H $\xrightarrow{\text{Hydrazine reductase}}$ Ammonia

Abel[50] postulated a hypothesis suggesting a role for leghaemoglobin in symbiotic nitrogen fixation. He assumes that an affinity exists between two leghaemoglobin molecules resulting in the formation of a complex which he calls ' cage ' or ' ferroenzyme '. A change in the configuration of the complex occurs as hydrogen is produced and nitrogen is reduced to ammonia. Nitrogen is bound by the cage (ferroenzyme) as soon as it enters the nitrogen fixing system. An electrostatic field between the iron-porphyrins (haemes) of the two leghaemoglobin molecules develops as a result of which each iron atom donates one electron to the nitrogen atom. The resulting ferrienzyme forms a stable complex with —NN— anions. The hydrogen present in the surrounding medium reacts with the anion to yield

diimide, HNNH. Diimide is quite unstable and, therefore, a change in the configuration of the cage becomes inevitable to form a stable complex of the diimide and the ferrienzyme. The conversion of diimide to ammonia through hydrazine and the subsequent release of the ammonia also involves further configurational changes in the ' cage '. At this stage, the ammonia formed will no longer bind itself to the ferrienzyme. Therefore, two moles of ammonia are released leaving behind the ferroenzyme (the cage). The stepwise reactions are schematically represented in Chart 1.

The ' cage ' may participate in subsequent cycles resulting in more ammonia production. The rate at which the cage or ferroenzyme could participate in the assimilation of nitrogen and its eventual conversion to ammonia are controlled by the rate of diffusion of protons and the competition of oxygen, carbon monoxide and nitrous oxide for similar sites on the haeme moiety of the haemoglobin molecule.

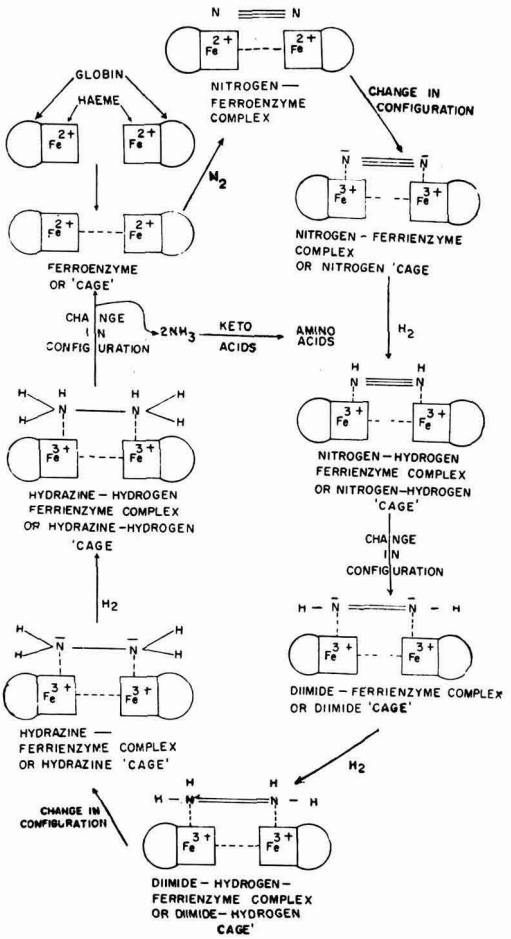

Chart 1 — Abel's hypothesis[50] concerning the participation of leghaemoglobin in symbiotic nitrogen fixation (schematically represented by the authors)

Burris *et al.*[51] were unsuccessful in detecting intermediate products between nitrogen and ammonia because nitrogen remained bound to the enzyme surface at the diimide-hydrazine levels and was released only by a reductive splitting of —N—N— bond with the formation of ammonia.

In spite of the ever-increasing knowledge about the biology of symbiotic nitrogen fixation, the precise mechanism underlying the participation of leghaemoglobin in the process still remains hypothetical. This situation is largely due to the elusive nature of the intermediary products between nitrogen and ammonia which precludes their detection. Therefore, it would be fitting to conclude with the remark of Ivanov *et al.*[44] that " it is still difficult to decide the role of leghaemoglobin as a component of nitrogen fixation in legume root nodules, and the role of hydrogenases and dehydrogenases in nitrogen reduction is not clear ".

Summary

The root system of plants belonging to the large botanical family Leguminosae possess distinct structures called ' nodules ' wherein the bacteria of the genus *Rhizobium* and the legume coexist in a symbiotic association resulting in the fixation of atmospheric nitrogen.

The nodules contain a red pigment, called ' leghaemoglobin ', which is not very different from animal blood haemoglobin, the prefix ' leg ' denoting its unique presence in Leguminosae. The molecular weight of leghaemoglobin is of the order of 16000-17000 while that of the blood haemoglobin is of the order of 66000. The pigment from soybean nodules consists of two distinct components of different electrophoretic mobilities. The possibility of this pigment acting as an oxidation-reduction catalyst and the assumption that it could form a metalloenzyme-nitrogen complex are the pivotal points in the major hypotheses concerning the role of leghaemoglobin in symbiotic nitrogen fixation.

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Seminar on Electrochemistry

The Central Electrochemical Research Institute, Karaikudi, is organizing the Eighth Seminar on Electrochemistry during 26-29 December 1967 at Karaikudi. There will be technical sessions on (i) electrode kinetics, electrochemical equilibria and electroanalyses; (ii) solid state electrochemistry; (iii) corrosion; (iv) electrodeposition and metal finishing; (v) batteries; (vi) electro-organic and electro-inorganic products; (vii) electrothermics and electrometallurgy; and (viii) techno-economic aspects of electrochemical process.

Abstracts of papers (not exceeding 300 words), in triplicate, may be sent to Dr P. B. Mathur, Convener, Eighth Seminar on Electrochemistry, CECRI, Karaikudi 3 (S. Rly), before 10 October 1967 and full papers, in duplicate, before 10 November 1967.

Approaches to the Chemotherapy of Cancer

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CLINICAL control of malignant disease may be approached by a number of possible routes, one of the more hopeful of which is cancer chemotherapy using a variety of compounds, viz. hormones, biological alkylating agents, antimetabolites, antibiotics, plant products and miscellaneous compounds.

HORMONE THERAPY

Hormones have long been regarded as growth-controlling substances and it was logical to try to alter the hormonal balance, in an attempt to treat tumours of the reproductive organs. Beatson[1] found that some mammary carcinomas regressed following removal of the ovaries. This ultimately resulted in the establishment of the relation between female sex hormones (estrogens) and cancer of the breast in women. The pioneer work of Lacassagne and later Huggins[2] established the relationship of male sex hormones (androgens) to the genesis of cancer of the prostate in men. Further Huggins and Bergenstal[3] discovered that genital cancer could be controlled at times by bilateral adrenalectomy. These results led to the development of the concept of 'hormone therapy', i.e. controlling the growth of cancer cells by stopping the supply of certain hormones.

Androgen Control Therapy

Role of Estrogens

In men, the chief sources of androgens are the gonads, and two methods have been developed to alter the endocrine environment of the tumour; the first is castration (orchiectomy) and the second is counterbalancing the influence of the male hormone by administering female sex hormones. In fact, the application of diethylstilboestrol against prostatic cancer[4] is still one of the most successful chemotherapeutic treatments of a neoplastic disease, although not a permanent one[5]. Other potent estrogenic agents are 17α-ethynylestradiol; its 3-methyl ether; 3-cyclopentyl ethers of 17α-ethynylestradiol and 17α-methylestradiol[6]; estradiol dipropionate and estrone sulphate. The treatment of the carcinoma of the prostate by estrogens causes painful breast enlargement and loss of libido in men, in addition to primary effects of nausea and vomiting. Therefore, in order to apply estrogens as antiandrogens, their undesirable feminizing potency must be minimized. With this aim in view, diethylstilboestrol diphosphate[7] and polyestradiol phosphate[8] (estradiol phosphate polymer, Estradurin) have been developed. Other important compounds with weaker estrogenic action and feminizing potency are 16α-methylestriol, its 3-methyl ether, 16α-chloro- and iodoestrones, and α-estradiol. The preparation and clinical use of the modified estrogens is certainly a step forward in this direction. The mechanism by which the estrogens act is not known. However, the estrogens act as powerful inhibitors of pituitary function[9].

Estrogen Control Therapy

Role of Androgens

A whole group of hormones produced in the ovaries, the adrenals and the pituitary are known to regulate the growth of female breast during puberty and its preparation for lactation during pregnancy. Cancer of the breast can be treated and sometimes cured by reversing the effect of some or all of these hormones. The palliative effect of ovariectomy (removal of ovaries) in breast cancer has already been discussed[1]. Nowadays either ovariectomy and adrenalectomy (removal of the adrenals) or hypophysectomy (removal of the pituitary) are used. The second line of approach is hormone therapy, i.e. giving male testicular hormone (testosterone) to women suffering from breast cancer. This is analogous to the hormone therapy of prostatic cancer in men. Testosterone propionate[10,11] is effective against certain types of advanced breast cancer and it is now a standard drug for evaluating the relative activity of new androgens. Its use is unfortunately limited due to the occurrence of less desirable sex effects in the women, viz. increased libido, hypertrophy of the genitals and hirsutism in addition to acne and lowered voice. Attempts have, therefore, been made to modify the structure of androgens to decrease their masculinizing effect or even to separate them altogether from their desirable antitumour action. These modified androgens then can be used as antitumour agents in female genital cancer. Thus 17α-methyl[12] and 17α-vinyl[13] testosterones, 17α-methyl-Δ^5-androstene-3β,17β-diol (MAD)[14,15], dihydrotestosterone[16], 2α-methyldihydrotestosterone propionate[17], 9α-fluoro-11β-hydroxy - 17α - methyltestosterone[18], 19 - nortestosterone[19] and Δ^1-testololactone[17,20] were developed. Of these, 2α-methyldihydrotestosterone propionate, or Metholone showed short-duration very high remission rate in breast cancer and Δ^1-testololactone produced effective remissions in a limited number of patients with advanced breast cancer without causing any masculinizing or other undesirable hormonal effects[21].

According to Segaloff[9], the clinical usefulness of the androgens in female breast cancer has been related directly to their androgenicity[15].

Role of Progestogens

Segaloff *et al.*[22] have described the use of 9α-bromo-11-oxoprogesterone[23,24] in the treatment of breast cancer. Progesterone and 17α-hexanoyloxyprogesterone have been used in the treatment of the carcinoma of the endometrium[25]. The remissions with these progestational agents have been long lasting and with less marked side effects.

Role of Adrenocortical Hormones

The adrenocorticoids, e.g. cortisone and its derivatives, and ACTH (adrenocorticotropic hormone) are useful in cancer chemotherapy. Cortisone and cortisol (hydrocortisone) are used in the control of acute leukaemia, in conjunction with Amethopterin and 6-mercaptopurine. Massive doses of ACTH and corticosteroids often produce remarkable remissions in chronic lymphatic leukaemia[26] and malignant lymphomas[27].

17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione (prednisone, Meticorten) has been found to produce fewer side effects and rapid remissions of short duration in acute childhood leukaemia. This compound has also shown some effects in acute leukaemia in adults[28]. In conjunction with 6-mercaptopurine and Amethopterin, prednisone is now effectively used in the control of acute leukaemia[29].

9α-Fluoro-11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione, oxylone, is a new synthetic high potency corticosteroid, which has demonstrated antitumour activity[30,31] against P1798 malignant lymphoma, sarcoma 180 and carcinoma 755. It has also been used in children with acute leukaemia[32] and as a palliative drug in some patients with breast cancer and colonic neoplasms[30]. A recent report, however, showed no objective remissions with patients having a variety of malignant tumours and the compound was found to bring about toxic effects, especially gastrointestinal complications[33].

Role of 2-(2-Chlorophenyl)-2-(4-Chlorophenyl)-1,1-Dichloroethane (*o,p'*-DDD)

o,p'-DDD, having structural similarity to DDT, has been found to be effective in patients with metastatic adrenal cortical carcinoma[34]. The treated patients responded to the drug with sustained reduction in adrenal steroid levels and one-third of the patients showed a decrease in tumour size[35]. These remissions have been maintained for quite a long time by repeated treatment with *o,p'*-DDD. The compound has been shown to be practically non-toxic and these findings have made *o,p'*-DDD a valuable drug in treatment of adrenal carcinoma.

Mechanism of Action

The mechanism of action of all these substances used in hormone therapy is still inadequate[15,36,37], though hormone therapy has been in use for well over twenty years. The results obtained in hormone therapy are unpredictable. In some cases estrogens inhibit while androgens stimulate tumours; in other cases the reverse is true. For example, breast cancers in women respond sometimes to androgens, sometimes to estrogens and at other times to either adrenalectomy or hypophysectomy. Similarly, in the majority of cases, patients with carcinoma of the prostate show improvement if estrogens are administered, but in others the androgens are known to bring about improvement. These difficulties encountered in hormone therapy of malignant tumours necessitate further improvements in this therapy to make it more effective.

BIOLOGICAL ALKYLATING AGENTS

Exposure to mustard gas is capable of producing systemic effects on the haemopoietic and especially the leucopoietic tissues and on the gastrointestinal tract[38-40]. Since leukopenia (a profound depression of white blood cells) would be an indication of improvement in leukaemia, bis-chloroethylsulphide was tested in leukaemic patients, as well as for the treatment of localized lesions of skin cancer[41]. In view of its toxic effects and vesicant action its use was abandoned. During the Second World War many new compounds were developed for the purpose of chemical warfare. Among these were the nitrogen analogues of mustard gas or the so-called 'nitrogen mustards', including the bis- and tris-2-chloroethylamines. It was soon recognized that these, like mustard gas itself, were not merely contact-vesicants, but could induce cytotoxic effects in a wide variety of tissues, and especially in those which are in a state of active proliferation[42]. Clinical studies[43-46] indicated their usefulness in Hodgkin's disease, lymphosarcoma, leukaemia and other related neoplastic diseases. bis-2-Chloroethylmethylamine hydrochloride (HN_2, chlormethine, Mustargen, Mustine, Embichin) has been the most widely used of nitrogen mustards. It has been used in the treatment of Hodgkin's disease, chronic leukaemias, lymphosarcomas and carcinomas of the breast, lung and ovary. It is still the drug of choice for the control of Hodgkin's disease. Unfortunately, it is toxic and possesses limited effectiveness against solid tumours. It can be reasonably said that the information gathered during the studies related to the physiological action of bis-2-chloroethylmethylamine on a large variety of neoplasms forms the basis on which cancer chemotherapy now stands.

Since the debut of HN_2 (ref. 40) many hundreds of biological alkylating agents have been synthesized with the objective of finding drugs, which are less toxic and more selective than the parent compound. Many of these new compounds are derivatives of HN_2. All these drugs have been shown to produce their biological activity by chemical reactions (characterized as alkylation) with essential functional groups in tissues. The drugs are, therefore, known as biological alkylating agents. The four important series of alkylating agents are: (i) the nitrogen mustards, (ii) diepoxides, (iii) di- and triethyleneimines and (iv) dimethanesulphonates.

Mechanism of Biological Alkylation

There are two generally recognized mechanisms for alkylation[47]. (i) Unimolecular nucleophilic substitution (S_N1), in which the rate-determining step is the ionization of a covalent bond, is aided by a polar solvent that solvates and stabilizes the resulting ions. The second step is a fast reaction of the carbonium ion (R^+) with a solvent molecule, or some new anion (Y^-):

$$R{-}X \xrightarrow{\text{slow}} \underset{\text{solv.}}{R^+} + \underset{\text{solv.}}{X^-} \quad (S_N1)$$

$$R^+ + Y^- \xrightarrow{\text{fast}} RY$$

$$\text{(or} \quad R^+ + HY \xrightarrow{\text{fast}} RY + H^+)$$

With alkylating agents reacting by S_N1 mechanism, the rate of reaction depends only on the concentration (and the solvent) and is independent of the concentration of Y^- (or HY). Thus

$$\text{rate} = K_1[RX]$$

(ii) Bimolecular nucleophilic substitution (S_N2) involves simultaneous bond-making and bond-breaking processes:

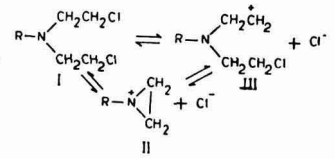
$$RX + Y^- \rightarrow RY + X^- \quad (S_N2)$$
$$(\text{or} \quad RX + HY \rightarrow RY + X^- + H^+)$$

The rate-determining step is the alkylation itself and the rate depends on the concentration and the structure of Y^- (or HY), in addition to the concentration of the alkylating agent. Thus

$$\text{rate} = K_2[RX][Y^- \text{ or } HY]$$

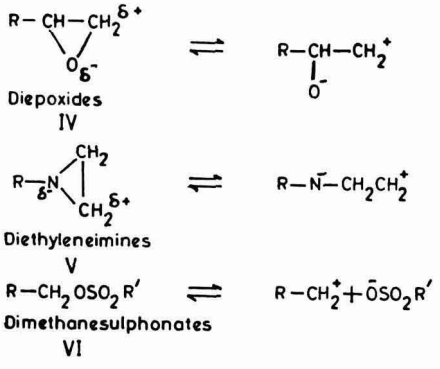
Some alkylating agents react by S_N1 mechanism, some by S_N2 and others by a combination of these mechanisms, depending on conditions of physiological *p*H and reactant concentration[48].

Aliphatic nitrogen mustards (I) rapidly form a stable cyclic ethylenimonium ion[49] (II) at physiological *p*H in aqueous solutions (and in polar solvents) by a unimolecular reaction. The cyclic imonium ion thus formed reacts with a nucleophilic centre by a bimolecular mechanism[50].



On the other hand, in the aromatic nitrogen mustards, e.g. chlorambucil $HOOC(CH_2)_3\text{-}C_6H_4\text{-}N(CH_2CH_2Cl)_2$, the nitrogen atom is weakly basic and is unable to form a stable ethylenimonium ion. These nitrogen mustards react with nucleophilic biological centres through a carbonium ion intermediate (III) (where R = aryl group) (S_N1 mechanism); the overall reaction rate is slower. These compounds represent an efficient class of biological alkylating agents because their reaction rate is independent of the concentration of nucleophilic sites.

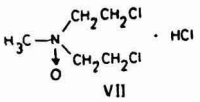
It is also possible to postulate an unstable reactive intermediate, the carbonium ion, with the diepoxides



(IV), the diethyleneimines (V) and the dimethanesulphonates (VI).

Nitrogen Mustards

bis-2-Chloroethylmethylamine N-oxide hydrochloride[51] (VII) (also known as Nitromin, Mustron, Mitomen, HN_2-oxide and Mustargen N-oxide) was



developed for clinical use by Yoshida and coworkers[52,53], who showed that it is less toxic and possesses higher therapeutic ratio than HN_2 (the therapeutic ratio of HN_2-oxide is 80, that of HN_2 being 17). Nitromin has been used to treat acute and chronic leukaemia, and a variety of solid tumours especially breast cancer. The occurrence of nausea and vomiting and the development of leucopenia are the undesirable side effects, but these are less pronounced than with HN_2 itself.

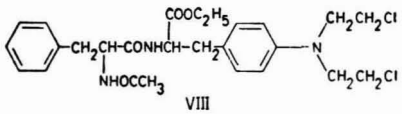
Another nitrogen mustard which has been studied extensively is *p*-bis-(2-chloroethyl)aminobenzylidenemalononitrile[54].

Everett *et al.*[55], while studying the effect of increasing water solubility in aromatic nitrogen mustards, synthesized 4-*p*-bis-(chloroethyl)aminophenylbutyric acid (CB 1348, chlorambucil, Leukeran). The use of this compound brought about beneficial responses[56,57] in patients with various lymphomas and leukaemias. It has been used successfully in the control of chronic lymphocytic leukaemia and in Hodgkin's disease and allied lymphomas[58-62].

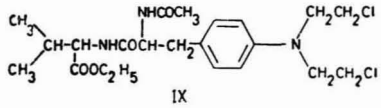
In order to take advantage of the naturally occurring amino acids as biological carriers, attempts were made to synthesize nitrogen mustards based on amino acids, which could act as carriers of cytotoxic groups. Amongst the earliest amino acid alkylating agents were N,N-bis-(2-chloroethyl)glycine and N,N-bis-(2-chloroethyl)alanine[63]. The latter compound induced remissions in various human leukaemias[64]. Further work in this direction led to the synthesis of 3-*p*-bis-(2-chloroethyl)aminophenylalanine by Bergel and Stock[65] in England and by Larionov *et al.*[66] in Russia. The *l*-isomer of the phenylalanine mustard is known as melphalan (L-sarcolysin), the *d*-isomer as medphalan and the *dl* form as sarcolysin or merphalan. So far melphalan and sarcolysin have been used clinically, especially in the treatment of malignant melanoma and multiple myeloma[67-71].

In search of improved drugs, a number of peptides of melphalan[72-75] and sarcolysin[76] have been synthesized, and two dipeptides have been found to be much less toxic. One is N-acetyl-*l*-phenylalanylmelphalan ester[72-75] (VIII) and the other N-3-*p*-bis-(2-chloroethyl)aminophenyl-N′-acetyl-α-alanylvaline[77] (IX).

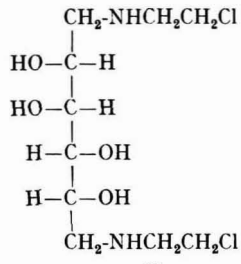
Working on the synthesis of alkylating agents with carrier moieties belonging to sugar-like polyols, Vargha and coworkers[78] synthesized 1,6-bis-2-chloroethylamino-1,6-dideoxy-D-mannitol (X) (Degranol, Mannomustine), which has been found to be effective in the lymphomas and leukaemias.



VIII

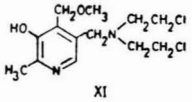


IX

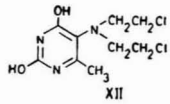


X

Other carriers have been used for the bis-2-chloroethylamino moiety. These include hydroquinone[79], chloroquine and quinacrine[80,81], pyridine[82], benzimidazole[83] and carbohydrates[84]. The derived compounds have shown inhibitory activity against animal tumours, but many other compounds using steroids[85–89] and terpenes[90] as carriers have been found to lack antitumour properties. On the other hand, the pyridoxine derivative[91,92] (XI) and the uracil mustard, 5-bis-(2-chloroethyl)amino-6-methyluracil[93,94] (XII) (dopan), have been used clinically and extensively studied.



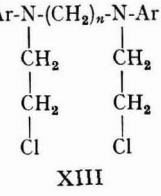
XI



XII

Chemical Structure versus Biological Activity

To exhibit cytotoxic activity, the compound must possess two reactive 2-halogenoalkyl groups[95,96], which should be an optimum distance apart. Thus, for the general structure (XIII), the compounds are active when $n = 2$ or 3.



XIII

With $n = 4$ there is a decrease in activity, and the compounds are inactive[97] when n is more than 4.

Further, the halogen atoms should not be separated from the nitrogen by more than two carbon atoms. The activity of these compounds can be satisfactorily related to the ease of hydrolysis of the halogen atoms in aqueous acetone. A study of a series of aromatic nitrogen mustards[98,99] showed that there is a correlation between ease of hydrolysis and biological activity. The analogues with low hydrolysis rates were found to be inactive against Walker carcinoma in rats, whereas those with 12 per cent or more hydrolysis in 30 min. in 50 per cent acetone at 66°F. were active.

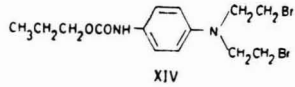
A few monofunctional alkylating agents show some anticancer activity, but most have no effect on experimental tumours. The bifunctional compounds are usually much more effective than the monofunctional ones. Seeking an explanation for this, Goldacre *et al.*[100] suggested that the two reactive arms might be required to permit the molecule to effect cross-linking, between two groups on a single surface or fibre, or between two contiguous fibres. Of the various possibilities cross-linkage between the complementary strands of the double helix of DNA is of particular interest[49,101,102]. Whether or not the cross-linking is essential for anticancer activity can be argued, but it was an hypothesis that led very rapidly to the application of diepoxides and di- and triethyleneimines as biological alkylating agents.

Drugs with Latent Activity

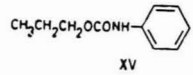
The principle of latent activity or latency means designing drugs carrying deactivated cytotoxic groups which could regain their activity by a process known to occur *in vivo*; the drugs will then show their full destructive effects at the sites most suitable to effect this activation.

One of the earliest approaches in this direction was the synthesis of derivatives of *p*-bis-(2-chloroethyl)-aminoazobenzene[103]. It was reasoned that *in vivo* reduction of the N=N bond of these inactive compounds would liberate *p*-amino-di-(2-chloroethyl)-aniline, or its derivatives, which would certainly show biological activity because of their high hydrolysis rates in comparison to the very low hydrolysis rates of the parent azo compounds. The realization proved successful, when a clear-cut correlation between ease of reduction and tumour-growth inhibition was established[103]. The most easily reduced member of the series was found to be *o*-(4-bis-2-chloroethylamino-*o*-tolylazo)benzoic acid, which has been given limited clinical trial[104].

Another interesting approach in this direction has been the use of a closely related substance capable of inducing the appropriate enzyme in the tumour, prior to the administration of the corresponding latent activity drug. N-(4-bis-2-bromoethylamino)-phenylpropylcarbamate (XIV) is itself incapable of causing complete regression of Walker 256 rat carcinoma, but it causes complete regression of 75 per cent of the test tumours in rats which have been pretreated with N-phenylpropylcarbamate[105] (XV).



XIV



XV

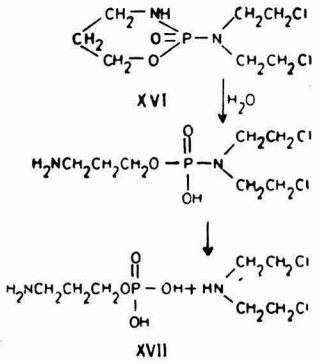
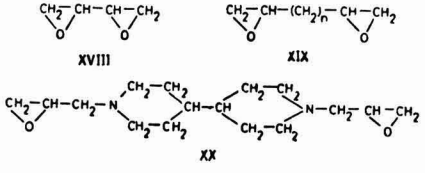


Chart 1 — Mechanism of the release of the active component of the drug (endoxan) *in situ*

1-bis-2-Chloroethylamino-1-oxo-2-aza-5-oxaphosphoridin (XVI) (endoxan, cytoxan, cyclophosphamide)[106], which is a cyclic phosphoramide derivative of dichloroethylamine, is one of the most widely used drugs. The rationale for the synthesis of endoxan came from the finding that abnormally high phosphoramidase activity existed in tumours[107], which might release the active component of the drug *in situ* through the mechanism shown in Chart 1. In fact, it has been shown that the drug is partially hydrolysed in the liver before liberating nor-HN_2 (XVII)[108], which is an active tumour inhibitor. It may be ranked with chlorambucil, Myleran, melphalan, TEM and the like in having limited but useful clinical application[109-115]. It has been reported that for maximum effectiveness, it requires the synergistic action of other compounds with antimetabolic or radiomimetic activity[116,117].

Diepoxides

The use of epoxides as tumour-growth inhibitors was in part suggested as the result of their earlier application in textile industry[118] for cross-linking wool fibres to prevent shrinkage. Ross[119] showed that epoxides also react with ionized acid groups, through a carbonium ion mechanism. They differ from nitrogen mustards, in that they react by the S_N2 mechanism, whereas the latter react by S_N1 mechanism. 1,2,3,4-Diepoxybutane (XVIII) is tumour inhibitory, in both *dl* and *meso* forms, the *dl* form being much less toxic[120]. The latter has been found useful in the treatment of Hodgkin's disease. If the epoxy groups are joined together (as in XVIII), or are separated by one or two methylene groups (XIX, $n = 1$ or 2), the activity is high whereas with an increasing number of methylene groups (n = more than 2), the activity is gradually diminished[118].

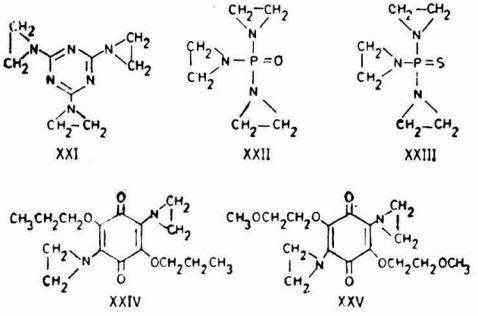


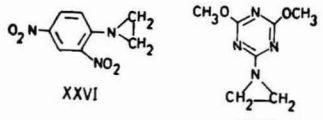
A series of basic diepoxides is of special interest, and of these 1,1′-bis-2,3-epoxypropyl-4,4′-dipiperidine, Eponate (XX)[121], is most promising. The dipiperidyl moiety makes it a basic compound. Because of its enhanced reactivity in acid solution, Eponate might concentrate preferentially in the more acidic tumour tissue and thus possess selectivity of action.

Ethyleneimines (Aziridines)

Prior to the discovery of their antitumour effects, the ethyleneimines were used in textile industry as cross-linking agents capable of effecting a great reduction in the swelling properties of natural as well as artificial fibres. Furthermore, the observation that N-mustards cyclize to give ethyleneimonium ion (II) led many groups of workers[122-130] to think that ethyleneimines might possess reactivity towards nucleophilic reagents similar to that of the nitrogen mustards and epoxides, and thus possess similar cytotoxic action. This line of thought resulted in the synthesis of one of the first ethyleneimine derivatives, 2,4,6-triethyleneimino-*s*-triazine[124-134] (XXI), triethylene-melamine, TEM. This can be administered orally and is an active anticancer agent, but appears to be more toxic[135,136] than HN_2 in the treatment of chronic leukaemias. Several other compounds of this type have been synthesized and shown to be useful clinically. The most important are triethyleneiminophosphine oxide (XXII) (TEPA)[137-141], triethyleneiminophosphine sulphide[142-150] (XXIII) (thio-TEPA, TSPA), DEPA, oxa-DEPA (OPSPA), and aze-TEPA[151-157]. TEPA (XXII), DEPA and oxa-DEPA have been discarded in favour of more stable thio-TEPA (XXIII). It has been used for the treatment of Hodgkin's disease, cancer of the stomach and mammary cancer.

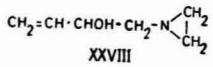
Other useful compounds in this group are the benzoquinone derivatives, E-39 (3,6-diethyleneimino-2,5-dipropoxybenzoquinone, XXIV), A-139 (3,6-diethyleneimino-2,5-dimethoxyethoxybenzoquinone[158-161], XXV) and Trenimon (2,3,5-triethyleneimino-1,4-benzoquinone[162]). E-39 (XXIV) and A-139 (XXV) can be given orally, intravenously or intratumourally and are effective against Hodgkin's disease, cancer of the stomach and chronic leukaemias (myeloid and lymphoid). A-139 (XXV), in which the propoxy side chains of E-39 (XXIV) have been replaced by methoxyethoxy side chains, is easily soluble in physiological saline, due to the solubilizing effect of the oxygenated side chains and is usually preferred. Trenimon has also shown usefulness in clinical trials.





XXVI

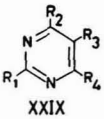
XXVII



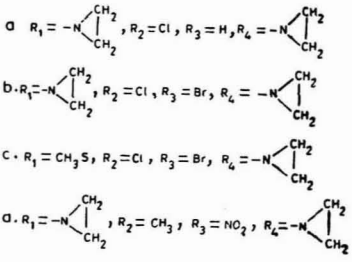
XXVIII

Two monoethyleneimine derivatives (XXVI, XXVII) have shown anticancer activity, but they are not very promising[163]. Another monofunctional compound, tetramin (XXVIII), has been used clinically[164,165]. Strictly speaking, compounds (XXVI), (XXVII) and (XXVIII) may not be monofunctional, because the carrier groups in (XXVI) and (XXVII) possess protein associating properties, and the double bond of (XXVIII) could undergo *in vivo* epoxidation or some other reaction after its ethyleneimine group alkylates a biological centre[163].

In an attempt to prepare compounds with a more favourable therapeutic index, the aziridinyl moiety has been attached to a pyrimidine ring, which is generally regarded as of more biological importance than the 1,3,5-triazine ring, e.g. (XXIXa)[166], (XXIXb)[167], (XXIXc)[167] and (XXIXd)[168].



XXIX



Dimethanesulphonates

Haddow and Timmis[169] showed that the property of biological alkylation could be made to associate with the ethyl groups in diethylarylamines by introducing aromatic sulphonic acid ester groups. Further development on these lines with considerable simplification of the bifunctional molecule resulted in the drug 1,4-dimethanesulphonoxybutane[170–173] (Myleran, busulphan, Myelosan). This compound has since been found useful in the control of chronic myeloid leukaemia[174–180].

1,4-Dimethylsulphonoxy-1,4-dimethylbutane (dimethyl Myleran, CB 2348) has also been evaluated clinically[181,182]. Another active compound in the series is nonane, 1,9-dimethanesulphonoxynonane[183–185], $CH_3SO_2O(CH_2)_nOSO_2CH_3$ (where $n = 9$). There is an interesting relationship between structure and activity. For example, all compounds of this formula where n = 2-10 show activity. The cytotoxic activity is a maximum when $n = 4$ (in Myleran), less when n = 5-8 and greatly reduced when n=2, 3, 9 or 10 (however, nonane appears to be exceptional).

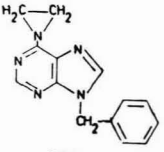
While working on the synthesis of sulphonic acid esters with carrier moieties belonging to sugar-like polyols, Haddow *et al.*[186] synthesized a relative of Degranol (X), 1,6-dimethanesulphonyl-D-mannitol (CB 2511, Mannitol Myleran), which is of use in chronic myelocytic leukaemia[187,188]. Another important achievement in this direction has been the development of 1,4-dimethanesulphonyl-L-threitol[189–191], which differs from the well-known drug Myleran only in the presence of two hydroxyl groups on the tetramethylene chain. This compound exists in the *l*, *d* and *meso* forms. The *d* form is inactive, while the *meso* form has about half the activity of the *l* form. In animal experiments, this compound showed antitumour activity, while showing only half as much toxicity as Mannitol Myleran. The inactivity of the *l*-isomer of Mannitol Myleran and *d*-isomer of this compound indicates that stereospecificity is of importance for the antitumour activity of the dimethanesulphonates having sugar-like polyols as carrying structures.

A few monoesters of methanesulphonic acid have shown activity against Walker 256 carcinoma in rats at high dose levels. Mention may be made of ethylmethanesulphonate[192,193] and 2-chloroethylmethanesulphonate[192,193]. The latter compound, being biologically more active, reacts *in vivo* with a cysteine unit in a protein to form *S*-2-chloroethylcysteine, which is more reactive than the parent compound. Thus, 2-chloroethylmethanesulphonate can be regarded as bifunctional, however, as *S*-2-chloroethylcysteine is inactive against Walker 256, its formation may not account for the anticancer activity of 2-chloroethylmethanesulphonate[194].

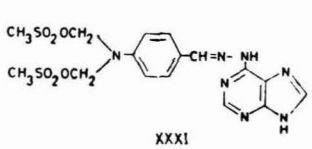
Hybrid Type of Tumour-inhibitory Agents

Other interesting carriers include purines. Of these the most important is 6-aziridino-9-benzyl-9H-purine[195] (XXX). This compound inhibits the growth of carcinoma 755 moderately well and that of Walker carcinoma 256 to a significant degree. The fact that (XXX) inhibits both carcinoma 755 (a purine-sensitive tumour) and Walker 256 (a tumour which is sensitive to alkylating agents but not to purines) underlines the conjecture that these compounds may be a truly new class of tumour-inhibitory compounds which combine an alkylating function with a metabolic carrier. The compound, therefore, might well be regarded as a hybrid of a purine antimetabolite and an alkylating group.

Another promising compound of this type, *p*-bis-2-methanesulphonyl-oxyethyl-aminobenzaldehyde-6-purinylhydrazone hydrochloride[196] (XXXI), has shown a remarkable biological specificity in completely destroying Yoshida hepatoma while showing



XXX

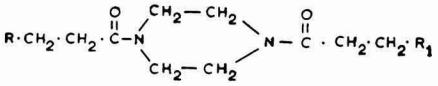


XXXI

little or no effect on other tumours[190] (Walker 256, Dunning leukaemia, Ehrlich ascites and Lymphoma 8).

Non-classical Alkylating Agents

The compound 1,4-bis-3-bromopropionylpiperazine[197,198] (XXXIIa, R = R_1 = Br) is a substituted diamide and hence does not fit the pattern of nitrogen mustards. The substance has been found effective in human chronic granulocytic leukaemia[190,199-201], and it appears that most probably its activity is due to alkylation under physiological conditions. For this reason, it has been classified as a non-classical alkylating agent. Replacement of bromine atoms by chlorine atoms does not effect the activity of (XXXIIa), whereas their replacement by methanesulphonyloxy group ($-OSO_2CH_3$) makes the resulting compound (XXXIIb) superior to all the above-mentioned compounds and also to Myleran[202,203]. Replacement of piperazine moiety in (XXXIIa) by ethylenediamine and trimethylenediamine does not affect the activity of the new compounds[202,203].



XXXII

a, R = R_1 = Br; b, R_1 = R = $-OSO_2 \cdot CH_3$

Effects of Alkylating Agents in Biological Systems

Examples of the most important nucleophilic centres encountered in biological systems are organic and inorganic anions, and amino and sulphydryl groups. Alkylation of carboxyl groups[204-210], amino groups[211-213], thiol groups[214,215] and phosphoryl groups[216-218] has been accomplished *in vitro* under conditions of physiological *p*H and temperature; alkylation of thiol groups proceeds at a *p*H higher than physiological *p*H. However, later findings[219,220] indicate that thiol groups in proteins in natural environment might be more reactive at the physiological *p*H and thus undergo ready alkylation.

It appears that the reaction of alkylating agents with phosphate groups in nucleic acids may be responsible for their biological action. Reactions of biological alkylating agents, with primary and/or secondary phosphoryl groups of naturally occurring nucleic acids[221-223], leads to the formation of unstable phosphate triesters in which an oxygen, sulphur or nitrogen atom is present in a β-position with respect to the ester linkage[224]. The hydrolysis of these esters results in the breakdown of the nucleic acid structure.

The purine and pyrimidine bases in naturally occurring nucleic acids are other centres where alkylation can take place. It is quite possible that the DNA of the cell nucleus is highly sensitive to the action of alkylating agents[225-229], which attack the 7-nitrogen of the guanine moiety[230,231]. In some cases the biological alkylating agents form an unstable intermediate with the phosphate moiety of DNA, which in turn attacks the N_7-atom of guanine[232]. The alkylation of guanine moiety results in the breakdown of the alkylated product with the release of guanine and the formation of labile apurinic acids[233,234]. The breakdown of the guanylic acid unit (XXXIII) of DNA (Chart 2) is an example of this type of molecular degradation[235].

If the alkylating agents are bifunctional, products like (XXXV, R = $-CH_2CH_2SCH_2CH_2Cl$ or $-CH_2CH_2CH_2CH_2OO_2SMe$) could associate with receptors in enzymes involved in purine metabolism and subsequently become firmly attached to the enzyme surface by alkylating an adjacent site. The deleted guanine derivatives (XXXV, R = $-CH_2CH_2SCH_2CH_2Cl$ or $-CH_2CH_2CH_2CH_2OO_2SMe$) will then function as competitive antagonists or irreversible antimetabolites[236].

It has been shown[237,238] that alkylating agents readily attack nucleic acids at the guanine component, both in the free state and in nucleoprotein complexes.

Roberts and Warwick[239] have established the alkylation of sulphydryl groups (Chart 2) by studying the interaction of Myleran (labelled on 2 and 3 positions, XXXVIII) with thiol groups of essential proteins and peptides (such as reduced glutathione or cysteine, as in XXXIX), through an elegant use of the techniques of autoradiography and paper chromatography. The first interaction product, a thiophenium ion (XL), is formed by the cyclic dialkylation of the sulphydryl group which breaks down giving rise to

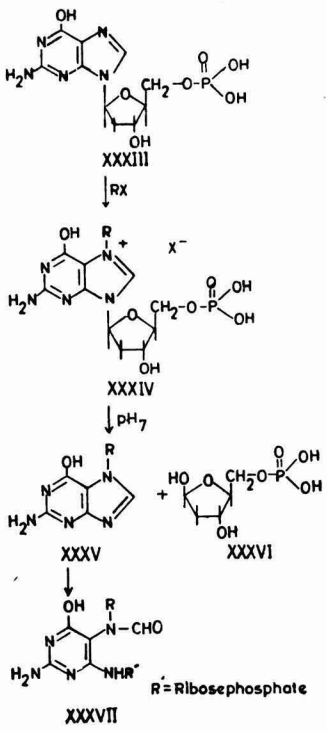


Chart 2 — Degradation of guanylic acid unit (XXXIII) of DNA

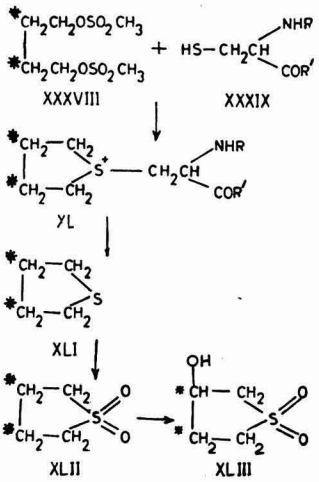


Chart 3 — Alkylation of Myleran (XXXVIII) with thiol groups of proteins or peptides such as reduced glutathione (XXXIX)

tetrahydrothiophene (XLI), which is biologically oxidized first to the corresponding sulphone (XLII) and then to 3-hydroxytetrahydrothiophene-1,1-dioxide (XLIII) which is excreted in urine. There is no evidence, however, to show any correlation between the suggested mechanism and the anticancer effects of Myleran. Similarly, administration of sulphur mustard gas, or a monofunctional nitrogen mustard, and subsequent examination of the urine of rodents has shown that alkylation of protein thiol groups is responsible for major constituents of urinary metabolites[240,241].

To sum up, one can say that the alkylating agents are capable of reacting either with the guanine moiety of the nucleic acid or protein thiol groups, but it is difficult to say which is responsible for the anticancer activity of the drugs. Nevertheless, these findings have helped considerably in our understanding of a part of the mechanistic role of the biological alkylating agents and thereby in our continued search for better alkylating agents.

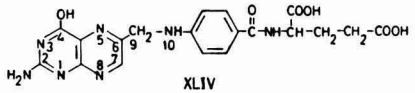
ANTIMETABOLITES

Alongside the alkylating agents came the development of metabolite antagonists (antimetabolites) or enzyme inhibitors. The most important antimetabolites having anticancer activity are analogues of nucleic acid bases, of folic acid and of glutamine. According to the antimetabolite theory of Woods and Fildes[242], antimetabolites might be obtained by simple modifications in the structures of known metabolites. This development resulted in the synthesis of numerous analogues of essential metabolites[243,244], some of them being chemotherapeutic agents. The studies related to this group of anticancer drugs have made many contributions to our basic knowledge of the biosynthesis of purines, pyrimidines and nucleic acids.

The exogenously supplied antipurines and antipyrimidines in carcino-chemotherapy interfere with nucleic acid biosynthesis by their metabolic incorporation into a fraudulent DNA (or RNA), thereby providing the cell with the wrong precursors, which prevent normal metabolic activity of the cells, or else their presence would competitively inhibit the incorporation of the normal metabolite and so hold up biosynthesis at that point. In certain cases, they upset the protein synthesis or interfere with the enzyme systems, which are themselves not involved in nucleic acid synthesis but are normally concerned in the biosynthesis of nucleic acid from the normal purines and pyrimidines. Thus it has been suggested that 6-mercaptopurine acts as a tumour inhibitor by inhibiting the synthesis of nicotinamide-adenine-dinucleotide[245]. The result of the antimetabolites should thus be inhibition of growth independent of their mode of action.

Folic Acid Analogues

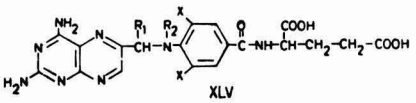
Folic acid (pteroylglutamic acid, XLIV) and its precursors play a vitamin-like role in the production and maturation of red blood cells and its deficiency causes the development of anaemia and severe cytopenia in animals.



From a study of the chemistry, biological role and metabolism of folic acid and its coenzyme forms[246-251], it is clear that to become active as a coenzyme, folic acid must first be reduced to tetrahydrofolic acid. Two enzyme factors, viz. TPNH and DPNH, are involved in this reduction[252,253]. The tetrahydrofolic acid thus formed can be enzymatically formylated at the 10-position. Further, such reactions lead to the formation of N^5,N^{10}-methylenetetrahydrofolic acid, N^5,N^{10}-methenyltetrahydrofolic acid and other such cyclic derivatives. These are the active cofactors which are responsible for the conversion of glycinamide ribonucleotide to formylglycinamide ribonucleotide, 5-amino-4-imidazole-carboxamide ribonucleotide to 5-formamido-4-imidazole-carboxamide ribonucleotide and deoxyuridylic acid to thymidylic acid. Interference in the synthesis of cofactors responsible for these conversions, which are of vital importance to nucleic acid synthesis, can be effected by blocking the synthesis of tetrahydrofolic acid[254-256] or its formylation in 10-position.

Aminopterin and Amethopterin

In 1948, Farber and coworkers[257] noted that the administration of folic acid to leukaemic children failed to improve their anaemia and may possibly have accelerated the disease. This observation resulted in the application of antifolic acid compounds in the treatment of acute leukaemia. They reported temporary remissions in acute leukaemia[258] in children produced by folic acid antagonist, aminopterin (4-aminopteroylglutamic acid, XLV).



XLV

a, R_1, R_2, X = H
b, R_1, = H, R_2 = CH_3, X = H
c, R_1, R_2 = CH_3, X = H
d, R_1 = CH_3, R_2, X = H
e, R_1,R_2, X = H and the glutamic acid residue replaced by aspartic acid
f, R_1 = H, R_2 = CH_3, X = Cl
g, R_1 = H, R_2 = CH_3, X = Br

This finding was of great importance as it gave a tremendous impetus to the study of folic acid antagonists as well as to cancer chemotherapy as a whole. Out of many analogues of folic acid[259,260], amethopterin (methotrexate, 4-amino-N^{10}-methylpteroylglutamic acid, XLVb)[261] is the most successful and it is now a standard drug. Amethopterin is the only known drug which cures the choriocarcinoma of the pregnancy state[262-265]. In combination with 6-mercaptopurine and cortisone, it eradicates all symptoms and laboratory evidence of acute leukaemia in some children. Unluckily, this cure is not a permanent one and the disease not only returns but becomes resistant to antifolic acid drugs[266]. Other closely related but less effective antifolics are: (XLVc)[267], (XLVd)[267], (XLVe)[268], (XLVf)[269] and (XLVg)[269].

The activity of these compounds depends upon their ability to inhibit the reduction of folic acid to tetrahydrofolic acid[254-256]. The deficiency of tetrahydrofolic acid causes inhibition of other reactions vital to nucleic acid synthesis. The antifolics may also interfere with the formylation of folic derivatives[270-275]. All these effects lead to impairment of nucleic acid synthesis with slowing down effects on cell division and growth.

Among other folic acid analogues mention may be made of napthopteridines[276-278], indolopteridines[278], 6,7-disubstituted 2,4-diaminopteridines[279-282], 2,4-diamino - 5 - phenylpyrimidines[283], arylazopyrimidines[284,285], phenyldihydrotriazines[286-290] and 8-aryl-8-azapurines[284,285]. None of the above-mentioned compound equals aminopterin or amethopterin in anticancer activity.

Purine Analogues

Adenine and guanine are the two purine bases present in the nucleic acid and a large number of compounds related to these have been synthesized and tested as purine antagonists.

Mercaptopurines

6-*Mercaptopurine* — Hitchings and coworkers[291] first prepared 6-mercaptopurine (6-MP) and after preliminary studies[292-294], Burchenal *et al.*[295] found the drug effective in inducing remissions in acute leukaemia. It has been suggested[296] that 6-mercaptopurine is the drug of choice for the treatment of acute leukaemia in adults. It is widely used in the treatment of acute and chronic myelocytic leukaemia[297]. 6-Mercaptopurine ribonucleoside (6-MPR) has a better therapeutic index than 6-MP against the transplanted adenocarcinoma 755 in the BDF_1 mouse[298-305] because of a wider span between effective and toxic doses, and not because of increased tumour-suppressive activity at equimolar doses. However, the predicted value of the mouse-tumour-drug system for therapeutic index failed in clinical trials, the toxicity of equimolar doses of the two compounds being similar in most cases[306]. It has been shown that 6-MPR *in vivo* breaks down to 6-MP[307]. Studies with both microbial and mammalian systems, including tracer studies with various purine nucleotide precursors, have indicated that 6-mercaptopurine, presumably as the nucleotide, interferes with purine interconversions known to occur at the nucleotide level[308]. However, Atkinson and Murray[309] have recently shown that 6-MP, without conversion to the corresponding nucleotide, very strongly inhibits the incorporation of guanine and hypoxanthine (but not adenine) into nucleotides, and hence nucleic acids, by Ehrlich ascites tumour cells by inhibition of phosphoribosyltransferase enzymes. In this manner it may block the utilization of purines by the cells.

Among other active derivatives of 6-MP, mention may be made of 6-substituted compounds (XLVIa, b, c)[301-304], 9-alkyl derivatives (XLVId, e, f, g)[310], 6-methane sulphonylpurine and purine-6-sulphonamide[311]. None of these compounds were better than 6-MP.

Recently, 6-methylthiopurine ribonucleoside[312] (XLVIh) has been shown to possess *in vivo* high activity against human cancer cells resistant to 6-MP and deserves clinical trials against MP-resistant acute lymphatic and chronic myelocytic leukaemia.

XLVI

a, R_2 = H; R_1 = Me
b, R_2 = H; R_1 = $CH_2C_6H_5$
c, R_2 = H ; R_1 =
d, R_1 = H; R_2 = Et
e, R_1 = H; R_2 = iso-C_3H_7
f, R_1 = H; R_2 = C_4H_9
g, R_1 = H; R_2 = cyclo-C_5H_9
h, R_1 = SCH_3; R_2 = β-D-ribofuranose

6-*Thioguanine* —Thioguanine (TG) is another active compound[293,294,296,313-316] in this series. Its action is similar to that of 6-MP. The tumour-inhibitory action[317-323] of thioguanine is primarily due to its incorporation into nucleic acids as thioguanylic acid. One of its derivatives, 2-amino-6-(1-methyl-4-nitro-5-imidazolyl)-thiopurine (ITG, imidazolylthioguanine), has been shown to have antitumour activity against a variety of transplantable rodent tumours. Its chemotherapeutic index is superior to that of thioguanine (TG) in adenocarcinoma 755 when given orally[324]. It has also shown favourable results in human chronic granulocytic leukaemia[325-328]. It was also possible to achieve tumour regression with ITG (administered

orally) in patients with inoperable metastatic squamous cell carcinoma of the oropharynx and larynx[329,330]. However, this tumour regression was accompanied by severe reversible bone marrow depression[330].

Azapurines

8-Azaguanine — The anticancer activity of 8-azaguanine[331] was first reported by Kidder *et al.*[332,333] and since then it has been found effective against a variety of neoplasms[334-339]. Azaguanine is incorporated into nucleic acids by replacing the natural base guanine, thus giving rise to ' fraudulent ' nucleic acid which is non-functional[308].

Among its derivatives mention may be made of 8-azaguanosine[340], 8-azaguanylic acid[340] and 8-azaxanthine[341], none of which are promising.

Other active azapurines are 2-azaadenine[342,343] and 8-azaisoguanine[344].

Other Purine Analogues

2,6-Diaminopurine — It is of importance that 2,6-diaminopurine[345] was the first purine analogue to show growth-inhibitory properties[346,347], and to be studied clinically[348]. Indirect evidence has been presented for its entrance into the cell and conversion to nucleotides[349], however, it does not lead to the mechanism of its action.

6-Chloropurine[350] showed remissions[317,351] in acute and chronic myeloid leukaemia. It appears that it is metabolized[352] in a similar way as 6-MP and that its conversion into nucleotide[353] may be essential to its activity.

Trimethylpurin - 6 - yl ammonium chloride, its 2-amino derivative and their 9-ribosides have shown significant activity[354-356] against carcinoma 755. Other derivatives of 6-chloropurine, however, showed no improvement in activity[300].

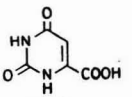
Purine, its riboside, 6-methylpurine, 2-fluoroadenosine[357] and 2-fluoroadenine[358] are only slightly active[301].

The adenine analogues, 4-aminopyrazolo (3,4-*d*) pyrimidines[359], were found[360] to be effective against resistant strains of adenocarcinoma 755 and leukaemia L1210 and L5178. However, these compounds were not put to clinical trials because they lead to severe liver toxicity. The antitumour activity and structural relationships of these and related compounds have been discussed recently by Robins[361].

Various purine nucleoside type antibiotics and active compounds prepared by changes in the carbohydrate moiety have shown antitumour activity. Important among these are puromycin[362], structurally similar aminonucleoside[363], cordycepin[364-366], 3′-amino-3′-deoxyadenosine[367-369], tubercidin[370] and 6-amino-9-D-psicofuranosylpurine[371] (pscicofuranine). The latter compound has been found to be very active in animal experiments. Apart from its antitumour activity, pscicofuranine is the first nucleoside to destroy bacteria in living animals.

Pyrimidine Analogues

The important pyrimidines in nucleic acids are uracil, thymine and cytosine. Of these uracil is present in RNA, thymine in DNA and cytosine is found both in DNA and RNA. Another pyrimidine of great importance is orotic acid (XLVII). Although it is not found in either DNA or RNA, it is the principal precursor of all the above-mentioned nucleic acid pyrimidines.



XLVII

Fluorinated Pyrimidines

5-Fluorouracil — 5-Fluorouracil[372,373] (5-FU) is an antimetabolite, the first in a series of fluorinated pyrimidines, with a structural formula closely resembling uracil. It has been extensively studied[374-381] and clinically used on thousands of patients. In spite of the toxicity shown by 5-FU at the therapeutic dose, it is gradually gaining a place among carcino-chemotherapeutic agents for the treatment of carcinomas of breast, colon and liver and other disorders[382-395]. Its tumour-inhibitory action is produced by active blocking of the thymidylate synthetase reaction in which deoxyuridylic acid undergoes methylation to give thymidylic acid[396]. For this purpose it is anabolized to its nucleotide metabolite 5-fluorouridylic acid[397-404].

Other related compounds prepared are 5-fluorouridine and 5-fluoro-2′-deoxyuridine[372,373], the latter compound being the most effective[405]. It has been used clinically[405]. 5-Fluoroorotic acid also possesses anticancer activity.

Fluorocytosine and its derivatives are similar in metabolism and in mode of action to fluorouracil compounds. The parent compound is inactive but 5-fluorocytidine and 5-fluoro-2′-deoxycytidine are active[406-408], the latter being the most active of all. It has been shown that 5-fluoro-2′-deoxycytidine acts by inhibiting the incorporation of orotic acid and stimulating the incorporation of thymidine into DNA[409,410].

Azapyrimidines

Replacement of one carbon atom and its associated hydrogen, in the pyrimidines, by the isoteric atom nitrogen results in a series of triazines, with considerable interest as potential chemotherapeutic agents.

6-Azauracil — 6-Azauracil has been intensively investigated. Unfortunately, it causes a variety of central nervous system disturbances in man[411,412]. Further work showed that it is inactive unless converted to its ribonucleotide[413]. These facts led to the synthesis of its ribonucleoside, 6-azauridine, which does not produce any significant disturbances of the central nervous system in man, and brings about temporary and incomplete remissions in various types of leukaemia[414]. Further improvement led to the synthesis of the orally administered 2′,3′,5′-tri-O-acetyl-6-azauridine.

6-Azacytosine[415] and its riboside, 6-azacytidine[416], are effective inhibitors of carcinoma 755, the latter being superior in its action. Both the compounds have low toxicity. 5-Azauracil and 5-azaorotic acid have shown some activity[415] but are inferior to 6-azauracil derivatives.

Other Pyrimidine Analogues

Among halopyrimidines (other than fluorinated pyrimidines), mention may be made of 5-chlorouracil, and the deoxyribosides of the 5-bromo- and 5-iodouracils[417,418]. Of these 5-iodo-2′-deoxyuridine[419] was found to be the most promising.

Other pyrimidine derivatives worth mentioning are 5-amino- and 5-hydroxyuridines[420], 4-thiouracil and uracil-5-carboxylic acid[415], 5-diazouracil[421], 4-amino-2-methylthio-5-pyrimidinemethanol[422], 1-β-D-arabinofuranosylcytosine[423] and Amicetin. The last compound which is an antibiotic[424] is a derivative of cytosine[425]. It has shown some activity in experimental systems[426].

Amino Acid Antagonists

Glutamine Analogues

Glutamine is essential for the introduction of amino groups in at least three stages in the *de novo* synthesis of nucleic acid in the living cell. Two antitumour agents, which are antibiotics, act as glutamine antagonists. These are azaserine and 6-diazo-5-oxo-L-norleucine (DON). These compounds were extensively studied, but their clinical trials were rather disappointing.

Among other antibiotics containing a diazo moiety, mention may be made of alazopeptin[427] and duazomycin A (N-acetyl DON)[428], both of which, like azaserine and DON, inhibit purine synthesis.

Glutamic acid-5-hydrazide (γ-glutamylhydrazine) is another glutamine antagonist[429] and so is structurally related γ-glutamylhydroxamate[430].

Other Amino Acid Analogues

A number of other amino acid analogues have been prepared with the idea that they might interfere with metabolism of the essential amino acids in tumour cells and thus act as competitive antagonists[431].

Ethionine, the ethyl analogue of methionine, possesses little anticancer effect and is too toxic. In view of the fact that leukaemic leucocytes require L-cysteine for their growth, Weisberger *et al.*[432] reported a number of cysteine analogues, in which sulphur has been replaced by selenium. These compounds have shown some inhibitory effect in human leukaemia[433] and other malignancies[434]. In addition, some phenylalanine[435–437], serine[438] and tyrosine[439] antagonists have also shown activity in experimental systems.

Possible Antimetabolites

Urethane — Urethane (ethyl carbamate) has been used in the treatment of chronic myeloid leukaemia[440]. It has also been utilized extensively in the treatment of multiple myeloma. Its activity appears to be due to its interference with the biological formation of ureidosuccinic acid[441].

Formamide and N-methylformamide have been found to possess antileukaemic property and the mechanism of their action appears to be similar to urethane[442].

Vitamin Antimetabolites

Many vitamin antagonists (especially of B-group vitamins) have been prepared, in the hope of finding new tumour-inhibitory compounds with selective action. The vitamins of B-group usually function as coenzymes of specific enzyme systems; therefore, these vitamin antimetabolites could be regarded as antagonists of coenzymes. None of the riboflavin antagonists, viz. diethylflavin, isoriboflavin, D-araboflavin and D-galactoflavin, dichloroflavin, have been found effective in clinicals trials.

Recently, 4-deoxypyridoxine (DOP) has been shown to bring about significant inhibition of sarcoma 180 in mice kept on a pyridoxine-deficient diet with overall very favourable therapeutic index[443]. The related compounds 3-deoxy- and 5-deoxypyridines and 5-deoxypyridoxal are more toxic than 4-deoxypyridine. Among other compounds 5-hydroxypropyl-pyridoxine[444] was more potent than DOP as an inhibitor of the growth of *S. Carlsbergensis* but ineffective in animal experiments against S-180. The closely related compound, 2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridine propionic acid ethyl ester[445], however, effectively induced lymphopenia in rats.

In addition to the above, antagonists of vitamin B_{12} also have been described.

Antimetabolites of Hexose Monophosphate Pathway (HMP) Intermediates

The main drawback of the antimetabolites described so far has been that they interfered with the normal processes also, and as such exhibited toxic effects. The development of an ideal cancer chemotherapeutic agent is made difficult, because of the fact that there are no clear-cut qualitative differences between the normal and the malignant cells which originate spontaneously. The differences so far discovered are all of a quantitative nature. Two of these are: (i) the low pyridine nucleotide (PN) levels, and (ii) the acceleration of hexose monophosphate (HMP) pathway in the tumour tissue. The possibility of preferential inhibition of tumour growth with antimetabolites of hexose monophosphate pathway intermediates was suggested by Sahasrabudhe[445]. In pursuance of this suggestion a number of five- and six-membered heterocycles were synthesized[446,447], out of which 2,5-thiophenedicarboxylic acid (TDA), 2,5-dimercaptomethylthiophene (MMT), thiouronium derivative of 2,5-dimercaptomethylthiophene (TUMMT) and 2,5-dicarbethoxy-3,4-dihydroxythiophene (Dicetol) were found to be effective against Yoshida (ascites) sarcoma and also against transplantable fibrosarcoma[448,449].

While studying the metabolism of Dicetol, it was suggested that this compound is degraded to an open chain compound, containing the lower half of the thiophene ring, composed of carbon atom Nos. 2 and 5 with their constituents and the sulphur atom, which is the main reactive component. Out of a number of analogues and derivatives of thiodiglycollic acid, synthesized and tested, thiodiglycollic acid (TDGA), thiodiglycol (TDGOL), and thiodipropionic acid (TDPA) showed good anticancer

properties (*see* ref. 449 and Sahasrabudhe *et al.*, unpublished data). These three compounds were able to completely annihilate the Yoshida sarcoma cells with only 10-days treatment. The treated animals survived their natural life span without any trace of malignancy. The corresponding Yoshida sarcoma transplanted control animals died within ten days. Dicetol and TDGA were tried in advanced and incurable cases. In cancers of the breast, lower jaw, head of the pancreas and stomach, subjective improvements were observed. Life expectancy was slightly enhanced. The growth of the tumour appeared to be slowed down, pain disappeared and the patients felt better. Recently, it has been shown that combined treatment with Dicetol and radiation may help in increasing the therapeutic effectiveness of radiation therapy in the treatment of malignant diseases[450].

ANTIBIOTICS

In view of the success of penicillin, streptomycin and other antibiotics in the control of bacterial infection, it is logical to search for antineoplastic activity in products from microbial systems. A number of antibiotics are described under the sections dealing with purine antimetabolites, pyrimidine analogues and amino acid antagonists. Other important ones are included here.

Actinomycin D

Actinomycin D and other actinomycins have a common chromophoric group, 3-amino-4,5-dicarboxy-1,8-dimethyl-2-phenoxazone. They differ in composition of their polypeptide chains attached to the chromophore through carboxyl groups. Thus actinomycin C differs from actinomycin D only in the substitution of D-*alloiso*-leucine for D-valine in the peptide chain. Actinomycins C and D both are active against various experimental neoplasms. Both are highly toxic. Actinomycin D has been most active in effecting temporary regression of metastatic Wilm's tumours in children[451-455]. Actinomycin D and other actinomycins appear to work by inhibiting the synthesis of RNA[456].

In the course of systematic search for new antibiotics exhibiting anticancer activity in animals and tissue culture, another actinomycin, actinomycin P_2, was discovered. This compound differs chemically from actinomycins C and D and has shown considerably less toxicity in animals than actinomycins C and D and is active against a variety of experimental tumours[457]. However, clinical trials on a small scale have shown little promise[457-460].

Mitomycin C

Antibiotics of this group were first described in 1956. Later Wakaki *et al.*[461] isolated the antibiotic designated as mitomycin C. Its structure[462] has been reported recently. Mitomycin C has been described as a radiomimetic agent because it can produce effects in microorganisms similar to those of ultraviolet light. It is an active compound and has been used clinically. The results with osteogenic sarcoma were the most promising[463]. Its inhibitory action is due to its capacity to bring about degradation of DNA.

Glutarimide Antibiotics

A number of antibiotics, all isolated from different *Streptomyces* species, have been found to possess glutarimide moiety in common. Important among these are actidione, streptovitacin A[464-466], E-73[467] and streptimidone [3-(2-hydroxy-7-methyl-5-methylene-4-oxo-6-nonenyl)-glutarimide[468]]. Streptovitacin A appeared to be one of the most potent anticarcinogens when tested in tissue culture[469,470]. Similarly, studies with E-73 indicated significant activity against mouse sarcoma 180 and against human tumour transplants grown in rats[466,471]. In spite of some favourable responses in human patients[472], streptovitacin A does not appear to be promising[473,474]. Clinical trials with dihydro E-73, i.e. 3-[2-(5-acetoxy-2-hydroxy-3,5-dimethylcyclohexyl)-2-hydroxyethyl]-glutarimide, brought about tumour regressions in some cases of squamous cell carcinoma of the lip, mouth, tongue and vulva[475]. It was necessary, however, to administer the drug by the isolation perfusion technique, as no objective evidence of improvement was noted when the drug was given systemically.

Other Antibiotics

Mithramycin — Mithramycin (PA-144) is derived from an actinomycete culture belonging to the genus *Streptomyces*. Its antibacterial activity is chiefly against gram-positive organisms. In spite of discouraging reports, mithramycin was re-evaluated in the treatment of disseminated cancer by Kofman and Eisenstein[476-478]. According to this study, mithramycin appears to have an important role in the treatment of some embryonal cancers. Mithramycin is also effective against some tumours metastatic to the central nervous system. It appears that further familiarity with this substance is necessary before the best results may be obtained.

Sarkomycin — Sarkomycin is a relatively unstable antibiotic and has been found active against Ehrlich ascites tumour. Dihydrosarkomycin also possesses anticancer activity. An isomeric compound, 5-methylenecyclopentanone-3-carboxylic acid is also an antitumour agent.

Daunomycin and rubidomycin — Daunomycin[479,480] and rubidomycin[481] are new antibiotics with antineoplastic action and appear to have identical physico-chemical and biological properties.

Other tumour-inhibitory antibiotics worth mentioning are chromomycin[482-484], actinogan[485-487], actinobolin[488], carzinophilin[489] and streptonigrin[490] and its methyl ester[491,492]. The therapeutic effects of streptonigrin[493] and its methyl ester[492] compare favourably with those of the fluorinated pyrimidine compounds. A distinct and important advantage of streptonigrin, given by prolonged infusion[493], over the fluorinated pyrimidine compounds is that it is without the disabling morbidity associated with the gastrointestinal toxicity of the latter. The compounds have a preferential deleterious action on DNA metabolism and net DNA synthesis practically ceases in the presence of streptonigrin.

PLANT PRODUCTS

A number of plant extracts have been tested for their antitumour activity. Colchicine has the ability to arrest mitosis of plant and animal cells. It has been extensively studied in cancer research. Its synthetic derivative, demecolcine (colchamine) is effective against chronic myeloid leukaemia, but only near toxic level[494]. Colchamine ointment has been found to cure skin cancer in the early stages[495]. Podophyllotoxin[496,497] is another antimitotic agent found in podophyllin resin, but clinical trials with this and its derivatives and analogues[498] have been disappointing[496-500].

Vincaleukoblastine (VLB; vinblastine)[501] and vincristine (VC; leurocristine)[501] are relatively new cancer chemotherapeutic drugs. These belong to a new class of dimeric alkaloids containing both indole and dihydroindole moieties and are extracted from *Vinca rosea* Linn., a common flowering herb known as periwinkle[502-507]. Both vinblastine (VLB) and vincristine (VC) completely suppress Hodgkin's disease[508], and produce profound remissions in lymphomas[509]. Vincristine is useful in acute lymphocytic leukaemia[501]. It is also helpful in the therapy of advanced breast cancer[510,511], and probably has its greatest value in secondary therapy after primary hormonal therapy fails[511]. Vinblastine, on the other hand, is also useful in choriocarcinoma[507,512,513] and adenocarcinoma[514]. VC is more active and more toxic than VLB. The mechanism of their action is still not clear; however, it appears that the activity of VLB is due to interference with cellular metabolic pathways[515].

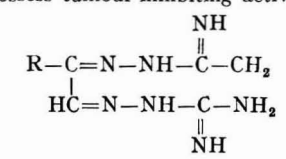
Some other alkaloids, e.g. emetine and narcotine, also exhibit antimitotic properties[266].

In view of the use of plant materials as therapeutic drugs, the Cancer Chemotherapy National Service Centre (CCNSC), USA, has undertaken systematic screening of world's plant products[516], which have been used in any form in the treatment of neoplastic and other related diseases in the past. As about 3 per cent of these plant extracts have shown activity[517], one might well hope to get some really worthwhile drugs from these natural sources in future.

MISCELLANEOUS COMPOUNDS

In addition to the above main groups of carcinochemotherapeutic substances, many other compounds have been tested on an empirical basis, and a few have been found to be active.

Methylglyoxal bisguanylhydrazone — After testing a series of guanylhydrazones, glyoxal bisguanylhydrazone (XLVIIIa) and the corresponding methylglyoxal bisguanylhydrazone (GAG) (XLVIIIb) were found to possess tumour-inhibiting activity[518]. The

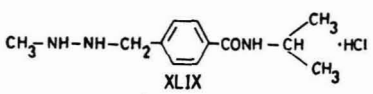


XLVIII

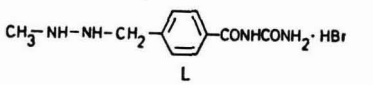
a, R = H; b, R = CH_3; c, R = $-CH_2CH_3$

latter compound also known as methyl GAG is most effective in acute myelocytic leukaemia[519], both in the child and the adult. Preliminary clinical trials in acute myelocytic leukaemia have demonstrated that methyl GAG effects a higher response rate than does 6-mercaptopurine, the previous drug of choice. It has two drawbacks: (i) it must be administered intravenously[520] and is inactive when administered orally, and (ii) it is quite toxic[521]. Hundreds of additional guanylhydrazones have been synthesized[522,523] and tested for anticancer activity; out of which only ethylglyoxal bisguanylhydrazone (1,1'-ethylethanediylidenedinitrilo-diguanidine, XLVIIIc) has shown activity.

Methylhydrazine derivatives — A new class of antimitotic agents (derivatives of methylhydrazine), which are of the general formula R—NH—NH—CH_3, where R represents a wide variety of organic radicals, particularly substituted benzyl groups have been recently synthesized[524] and found to have marked antitumour action. The most active of them are 2-*p*-isopropylcarbamoylbenzyl-1-methylhydrazine hydrochloride (MIH) (XLIX) and 2-*p*-allophanoylbenzyl-1-methylhydrazine hydrobromide[525] (L). MIH has been clinically evaluated against pulmonary tumours, breast cancer, testicular tumours and other types of solid tumours[526]. It has been claimed



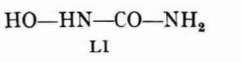
XLIX

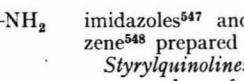


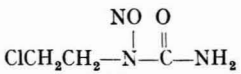
L

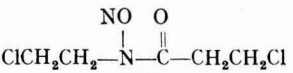
that MIH brought about unexpected therapeutic success in patients who were beyond surgical or radiologic treatment[526]. The results of clinical applications certainly indicate that MIH alone or in combination with 5-fluorouracil or any other antimetabolite is a useful agent in the treatment of solid tumours. It appears that these drugs act by markedly prolonging interphase[527] during cellular division and that only chromatid and no chromosome breaks occur. Further work[528] has revealed that the above-mentioned methylhydrazine derivatives modify the viscosity of aqueous solutions of DNA; and that this action is due to autoxidation of these compounds, leading to the formation of hydrogen peroxide. Since the action of hydrogen peroxide on DNA (leading to its degradation) proceeds via OH radicals, it is evident that the action of methylhydrazine derivatives on DNA is analogous to the indirect effect of ionizing radiation, which also acts mainly through OH radicals. Whether the inhibition of tumour growth depends on the action on preformed DNA, on the synthesis of DNA, or on other biochemical effects of the hydrogen peroxide is a problem which requires further investigation. Nevertheless, the mode of action of the methylhydrazines appears to be obvious.

Urea derivatives — Hydroxyurea (LI) was found to be active against transplantable mouse leukaemia L1210 and several other rodent tumours[529-531] but only moderately inhibitory in granulocytic leukaemia


LI

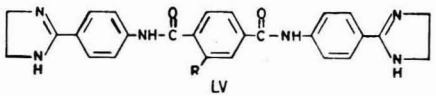

LII

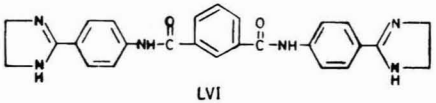

LIII


LIV

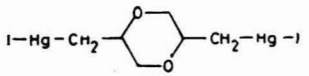
in man[532,533]. This demonstrated unquestionable antileukaemic effect of an entirely new class of chemotherapeutic agent. The mechanism of the action of hydroxyurea is not known but the pattern of clinical response to hydroxyurea to date suggests that its activity is more like that of an antimetabolite[534,535]. Other active urea derivative is 1-methyl-1-nitrosourea (LII) which has been shown to be antileukaemic[536]. This material passes the blood brain barrier and destroys leukaemic cells in the brain tissues. Its chief drawbacks are that it is extremely difficult to handle and decomposes at body temperature (37°C.). A number of nitrosoureas were then synthesized and tested[537-539], out of which 1-(2-chloroethyl)-1-nitrosourea[538,539] (LIII) and 1,3-bis-2-chloroethyl-1-nitrosourea[537,539] (LV) were found to be promising. These compounds are far more stable than 1-methyl-1-nitrosourea and still show high degree of efficacy in the intracerebral situation.

Phthalanilide derivatives — A group of terephthalanilide and isophthalanilide derivatives[540,541] (LV, R = H or NO_2 or Cl; LVI) have been found to show a high order of therapeutic activity against leukaemia[542]. Out of these 2-chloro-4′,4″-di-2-imidazolin-2-yl-terephthalanilide dihydrochloride (LV, R=Cl) and the corresponding imidazolin isophthalanilide (LVI) have shown striking properties[542,543].


LV


LVI

Bis mercurials — 2,5-Bis-iodomercurimethyl-*p*-dioxane[544] (LVII) is effective against carcinoma 755 and has shown potent specific inhibition of glycerophosphate dehydrogenase (50 per cent at $5\times10^{-6}M$). Its greatest drawback is its insolubility.


LVII

Triazenes and tetrazenes — Active compounds belonging to these groups are 3,3-dimethyl-1-phenyltriazene and its derivatives (R = Me or NO_2 in the benzene ring)[545,546], a few derivatives of triazenoimidazoles[547] and 1,4-dimethyl-1,4-diphenyl-2-tetrazene[548] prepared as early as 1878 by Fischer.

Styrylquinolines — Among these the most potent compound was found to be 4-*p*-dimethylaminostyrylquinoline[549].

1-*Aminocyclopentanecarboxylic acid* — This unnatural amino acid showed activity against experimental systems[550] but was found inactive in human cancer. However, it was found to possess the power to alleviate the excruciating bone pain associated with multiple myeloma[551].

3-*Ethoxy*-2-*ketobutyraldehyde* — 3-Ethoxy-2-ketobutyraldehyde[552] (kethoxal) and related compounds also possess carcinostatic action.

Conclusion

To sum up, there are three methods known to man for treating cancer; they are (i) surgery, (ii) radiation and (iii) chemotherapy. At present the cures represent a mere 35 per cent (brought about by the first two methods) of the total number of people suffering from cancer. For the remaining 65 per cent of cancer victims, cancer chemotherapy appears to offer the greatest promise. An attempt has been made to give an account of the different types of carcinochemotherapeutic agents. The ultimate achievement in cancer chemotherapy would be the development of a specific anticancer agent without any effect on normal tissues. Perhaps, in future, we may be able to develop such a compound, but the task is obviously not an easy one. Anticancer drugs, with some rare exceptions, do not produce a permanent cure. For a short while the tumour responds to the drug and then it develops resistance to it[308]. Another associated phenomenon is that of cross resistance[352,553]. In view of the above and the availability of agents which are not specific, it is desirable to use the selected drug in as high a dose as possible without increasing systemic toxicity, with the aim to damage abnormal tumour cells before the onset of resistance to the drug. There is a narrow difference between the effect of available drugs on normal and abnormal rapidly proliferating cells. Methods of administration that aim to exploit this difference are regional perfusion and intra-arterial infusion. In regional perfusion[554], a certain part of the body is isolated from the rest by clamping the main blood vessels and maintaining its blood supply by the use of an extracorporeal oxygenating circuit. This isolated region is subjected to a very high dose of the drug by introducing the drug into the extracorporeal circuit. Intra-arterial infusion[555], on the other hand, serves to introduce the drug slowly into the arterial supply to the tumour bed. Both these techniques minimize the toxic side effects of the drug and appear to be helpful in some situations[556-572]. In addition to these, replacement therapy, combined therapy[575], surgical adjuvant therapy, and combination with radiotherapy have been tried using various drugs and the results obtained are quite promising[553,573]. In addition, different types of approaches have been made towards achieving greater selectivity of action against tumour cells by carcinochemotherapeutic agents[574] and towards improving the existing methods of experimental evaluation of potential anticancer agents.

TABLE 1

Chemotherapeutic Agent	Types of human cancer in which it is effective
ACTH	Acute leukaemia
Actinomycin D	Wilm's tumour
Amethopterin (methotrexate)	Choriocarcinoma, acute leukaemia
Chlorambucil	Chronic lymphocytic leukaemia, ovarian carcinoma
6-Chloropurine	Acute leukaemia
Cortisone	Acute leukaemia
Cytoxan (endoxan, cyclophosphamide)	Lymphomas
o,p'-DDD	Adrenal carcinoma
Diethylstilboestrol	Prostatic carcinoma
5-Fluorouracil	Breast carcinoma, metastases from intestinal tumours
5-Fluoro-2'-deoxyuridine	Breast carcinoma, metastases from intestinal tumours
Hydrocortisone (cortisol)	Acute leukaemia
Melphalan	Lymphomas
6-Mercaptopurine	Acute leukaemias, chronic myelocytic leukaemia
2α-Methyldihydrotestosterone propionate (metholone)	Breast cancer
Methylglyoxal bisguanylhydrazone	Acute myelocytic leukaemia
Myleran	Chronic myelocytic leukaemia
Nitrogen mustard	Hodgkin's disease
Prednisone	Acute leukaemia
Progesterone	Carcinoma of endometrium with metastases to the lung
TEM	Lymphomas
Δ'-Testololactone	Breast carcinoma
Testosterone propionate	Breast carcinoma
Thioguanine	Acute leukaemia
Thio-TEPA	Lymphomas, in adjuvant surgery of mammary cancer in premenopausal patients
Urethane	Chronic myelocytic leukaemia, multiple myeloma
Vincaleukoblastine	Hodgkin's disease, lymphomas
Vincristine	Hodgkin's disease, lymphomas, acute lymphocytic leukaemia

A wider understanding of different types of cancer, from the viewpoint of origin, progress and control, has been extremely difficult so far. However, some achievements have been made and the gains have been substantial. A list of chemotherapeutic agents capable of producing remarkable remissions and of potential value in various forms of human cancer is given in Table 1.

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REVIEWS

THEORY OF RANDOM FUNCTIONS by A. Blanc-Lapierre & R. Fortet; translated by J. Gani (Gordon & Breach Science Publishers, New York), 1965. Pp. xxi+432

The theory of random processes plays a prominent role in the understanding of different types of phenomena in all branches of natural science. While the theory, being an extension of one of the well-developed branches of classical analysis (probability theory), can be regarded as an application of the theory of measure; it has been enriched to a very large extent by a study of the specific examples occurring in the realms of physics and engineering. That the axiomatic and phenomenological approaches to the theory are equally important from the viewpoint of the development of the subject is fully borne out by the book under review. As explicitly stated by the authors, this is a book for theoreticians of random functions, applied workers and physicists as well. The challenge of meeting the requirements of these different groups has been squarely dealt with by the authors. The translation of the original version, which appeared in French in 1953, is proposed to be carried out in two volumes, the first of which (under review) contains the following chapters: A practical introduction to the study of random functions; Axioms, basic concepts and fundamental theorems in the theory of probability; General introduction to random functions; General introduction to stochastic processes; Random functions with independent increments; Random functions derived from Poisson processes; Markoff processes; and Permanent discontinuous Markoff chains, permanent continuous Markoff chains, additive functionals of a Markoff process.

It is difficult to present an unbiassed review of the translation of a book whose original version has been and will continue to be a source of inspiration and guidance for workers in this field, including the reviewer. Nevertheless, the reviewer has taken the risk of making some observations. The first chapter contains a classic account of an innumerable number of physical phenomena that can be cited as examples of random functions, the noteworthy feature being the introduction of the notion of realized trajectory of a random process, a concept that has proved to be of great consequence in physical applications of the theory of random integration. Next, the definitions and fundamental results of probability theory are presented and axiomatic foundations of probability theory developed. The authors then proceed to a detailed account of the calculus of random functions with equal emphasis on the modes of proof and applications of the main results of the theory. An exciting and informative account of Poisson processes is presented in a manner that can be appreciated by a wide spectrum of scientists ranging from measure theorists to electrical engineers. The final chapters dealing with Markoff processes are exceptional in their character in that they bring out the original spirit of Kolmogorov's work and will enable future generations of probability theorists to experience the excitement to some degree of intensity with which Markoff processes have been first received.

The appendix gives an idea of the minimum mathematical background that workers in applied probability should possess in order that they be intelligible to the pure theorist.

Finally, the reviewer has a word or two about translation. The translator has expressed that he has attempted to retain the flavour of the original French. The original flavour would have still remained the same if some prepositions and adverbs like *pour, á, avec* and *si* had been translated. Among translator's list of books that have appeared since 1953, the reviewer has found a significant omission. The lucid, extensive article of Prof. Alladi Ramakrishnan on probability and stochastic processes that has appeared in *Handbuch der Physik* and that has, by its very akin nature to the book under review, proved to be very popular among probability theorists and physicists, has somehow failed to attract the attention of the translator.

S. K. SRINIVASAN

MODULATION, RESOLUTION AND SIGNAL PROCESSING IN RADAR, SONAR AND RELATED SYSTEMS by R. Benjamin (Pergamon Press Ltd, Oxford), 1966. Pp. xii+184. Price 55*s*.

The book is a recent and valuable addition to the literature on signal processing techniques. Recent advances in the field of signal processing methods have assumed considerable importance in techniques for improving the performance of radar, sonar and other systems. The author has tried to give a generalized treatment on those aspects of the signal processing which are common to radar, sonar and other related fields.

In the first chapter, which is an introductory one and very brief, some of the improvements sought after in pulse radar are enunciated. In the second and the third chapters, the concept of resolving and discriminating powers has been explained. In the fourth chapter, a general analysis has been given of the types of modulation employed in various systems and the process of detection of these types of modulation. In the fifth and the sixth chapters, the technique of pulse stretching and coherent recompression and the utility of this in signal detection has been analysed. The seventh chapter covers aspects of Doppler determination and also the general types of anti-clutter techniques. In the eighth chapter, the interaction that exists between modulation, data processing and aerial design has been brought out. The subsequent paragraphs cover such aspects as the characteristics of trains of modulated pulses, the technique of combining and processing ' noisy ' signal sources, logical and nonlinear processing, reception of signals of

large time-bandwidth product in a varying propagation path, etc.

The book is indeed a very original effort on the part of the author to bring in varied techniques of signal processing into a unified treatment, using minimum of mathematics and, at every stage, drawing upon basic concepts and physical principles.

The book would have been much more useful had the author given references to some of the related publications at the appropriate contexts. It would have also been useful if, in the initial chapters, the author had explained with suitable illustrations, the basic concepts of signal processing, both of the conventional and of the more sophisticated ones.

On the whole, the book is a very original treatment and is definitely a useful addition to the existing literature on signal processing techniques.

V. NARAYANA RAO

STATE VECTOR SPACES WITH INDEFINITE METRIC IN QUANTUM FIELD THEORY by K. L. Nagy (Akademiai Kiado, Budapest), 1966. Pp. x+131. Price $ 4.20

The notion of an indefinite metric in Hilbert space was utilized for the first time by Dirac in connection with the quantization of fields. Pauli studied it further, but perhaps one of the most fruitful of its applications was that by Gupta and Bleuler for the quantization of the electromagnetic field. In recent years, Heisenberg has employed it in his nonlinear theory for elementary particles in an attempt to eliminate the divergence problems of conventional field theory.

In the book under review, Nagy who has made many contributions to the subject provides a succinct account of the formalism and the applications of the indefinite metric in various physical contexts in quantum field theory. Two alternative ways of introducing the indefinite metric are discussed. In the first, a vector space is introduced in the usual fashion, except the condition that the norm of a vector is positive definite and that it is zero only if the vector is itself zero. Here negative norms and a null norm without vector itself being zero are also allowed. Pseudo-hermitian operators over this space are defined and the question of the completeness of the eigenvectors of an operator is studied at length.

In the η-formalism, the indefinite metric is introduced through a metric operator η which is hermitian and defined over the usual Hilbert space. Norms, scalar products and metric elements are defined with respect to this operator. The only example of this formalism given in the book is the case of the oscillator which by a change of sign of the commutation relation between the creation and annihilation operators involves the indefinite metric.

The examples from field theory considered are: (1) the oscillator with multipole and complex ghosts (states with non-positive definite norms), (2) the oscillator coupled to a fixed source, (3) a pseudo-scalar field with an equal time commutator which is not a δ-function, (4) the quantization of the electromagnetic field (the necessity for an indefinite metric arises because we wish to obtain the fourth component of the electromagnetic potential which is pure imaginary in classical theory as the eigenvalue of a hermitian operator), (5) field theories with higher order Lagrangians which arise, e.g. when one is using a $(2j+1)$ or $2(2j+1)$ formalism for particles with spin greater than one, (6) the Pauli-Villars regularization of propagators by the introduction of an appropriate superposition of auxiliary fields corresponding to different masses (the Feynman regularization corresponds to the simplest case of a single auxiliary field) and other regularization procedures like the Yokoyama and the Shimodaira models, (7) the Markov model where the necessity for an indefinite metric is not obvious, (8) Heisenberg's nonlinear theory where the ansatz for the commutator function already involves an indefinite metric, (9) Froissart's model, (10) Sudarshan's model of a scalar field coupled to a fixed source, and finally (11) the Lee model which was studied extensively by Pauli and Kallen and by Heisenberg.

The third section of the book deals with the probabilistic interpretation of a theory with indefinite metric. The decomposition of the whole space into physical and non-physical subspaces has to be done by using physical arguments. Among the models considered the problems of oscillators, quantum electrodynamics and Froissart's model are shown to be probabilistically interpretable. The conditions deciding the interpretability of a theory are investigated and the relationship between a nonlocal theory and a theory with indefinite metric is pointed out.

In the final section, the indefinite metric is considered briefly in the context of axiomatic methods.

The general style of the book is that of a collection of papers patched up, but this does not detract from the usefulness of the book for quantum field theorists.

K. VENKATESAN

CNS DRUGS — A SYMPOSIUM edited by G. S. Sidhu, I. K. Kacker, P. B. Sattur, G. Thyagarajan & V. R. K. Paramahamsa (Council of Scientific & Industrial Research, New Delhi), 1966. Pp. xv +367. Price Rs 33.00; $ 10.00; 66s.

This is a collection of papers read at an international symposium held at the Regional Research Laboratory, Hyderabad, India, during 24-30 January 1966. The volume records 32 contributions from distinguished chemists, pharmacologists and others drawn from UK, USA, France, Canada, Yugoslavia, Czechoslovakia, Germany, Italy and India. The papers cover a wide field of drugs effective on the central nervous system, drawn from natural resources and the synthetic field. The central theme of most of the papers is an attempt to bring about, as far as may be possible, an understanding of the mechanisms of action of the wide variety of CNS drugs and construct a basis for further investigations by discussing the relation of structure to activity (SAR). Experimental techniques and synthetic routes have been discussed in some of the papers.

The wide variety of organic structures which have been found to possess one or the other CNS activity does not permit escape from the conclusion that we have still a long way to go to define a given

biological activity in absolute structural terms. Structural configuration and conformation are indeed vastly important for a desired activity in a given class of organic compounds. However, whereas it is possible to determine accurately the detailed configurational aspects of a given drug molecule and its disposition in space, we have still to guess largely the corresponding bioreceptor. And, this is complicated further by the fact that mechanistic aspects of the so-called weak interactions and the hydrophobic bond, which must undoubtedly play a dominant role in specific drug receptor associations, are not fully understood at present. In this context, SAR tends to have only a fairly recognizable meaning. This, however, is the inherent handicap in drug research today. The authors of some of the papers have discussed SAR elegantly, though rather broadly and without material reference to the aspects outlined above, and valuable leads are visible in a number of contributions.

As one reads through this volume, one does indeed miss the discussions. It is conventional and certainly valuable that each symposium volume gives fair space to discussions after each paper. This indeed is important from the point of view of highlighting mechanistic leads and stimulating pointed interest in a given field, which is the most important aspect of a symposium.

The volume has been brought out very well indeed and has remarkably few mistakes. It would constitute a good addition to the libraries of laboratories engaged in drug research.

M. L. DHAR

RADIATION DAMAGE IN GRAPHITE by J. H. W. Simmons (Pergamon Press Ltd, Oxford), 1965. Pp. xii+242. Price 80s.

Apart from its importance in nuclear reactors, particularly graphite moderated ones, irradiation damage in graphite is of considerable interest to the solid state physicist and chemist. During the past twenty years, a large amount of data has accumulated on the changes in properties of graphite resulting from neutron bombardment and annealing of the damage caused. More recently, results of electron microscopic investigations on single crystals of graphite have appeared and these have added considerably to an understanding of the basic phenomena occurring in graphite used in reactors.

The book deals with all these aspects. It has been written more for the reactor physicist and engineer rather than for the theoretical physicist and chemist. After dealing briefly with the crystal structure and properties of natural and synthetic graphite in Chapter 1, the author gives in Chapter 2 a short systematic account of the effects of irradiation variables, such as neutron dose, neutron energy spectrum and temperature. Chapter 3 deals with the structural changes produced in graphite as revealed by X-ray diffraction and electron microscopic techniques. Chapters 4 and 5 deal with the effects of irradiation on the electrical, magnetic and thermal properties of graphite. From the reactor engineer's point of view, the dimensional changes and changes in mechanical properties on irradiation are of great importance and these are dealt with in Chapters 6 and 7. The last chapter deals with the phenomenon of stored energy, its measurement and release.

The book has a subject and author index, copious references to literature and illustrative figures and diagrams in each chapter. It will be most useful to those who wish to apply the results to practical reactor problems, but will also be of interest to students and teachers of solid state physics.

JAGDISH SHANKAR

INTERPRETATION OF MASS SPECTRA by Fred W. McLafferty (W.A. Benjamin Inc., New York), 1966. Pp. 229

This book, written by one of the pioneers in the field of organic mass spectrometry, is the outcome of a course in mass spectrometry given six times to a total of 600 scientists. The orientation of the book is more practical than theoretical. The author has beautifully illustrated how one of the major aids in understanding mass spectrometry is to learn to solve unknown spectra. As the author himself points out " in contrast to the books that give detailed descriptions of the mass spectra of particular types of compounds, the present publication has been designed to teach the interpretation of mass spectra with emphasis on the identification of unknown compounds ". The objective of this book appears to be to demonstrate how the ' jigsaw puzzle ' fragments of varying masses can be intelligently and successfully put together to construct a working molecular structure.

In the introductory chapter, the reader is given an opportunity to familiarize himself with the mass spectra of organic compounds. How the information on the molecular weight and molecular formula can be obtained from the spectrum is discussed briefly in the next chapter.

In the subsequent chapters (3-7), the author deals with radical ions, the general appearance of the spectrum, even electron ions, neutral fragments and postulations of ion structures. Considering the vast scope of the subject matter and the aims as stated, it is not unexpected that the depth of treatment is limited here.

The following chapter contains the mechanisms of unimolecular ion decomposition reactions. Instead of cataloguing many mechanisms, an attempt has been made to classify them into a few general categories. These generalizations are very helpful in spectral interpretation. Odd and even electron ions are well described and illustrated. Their decompositions are very clearly presented.

The ninth chapter deals with molecular structure postulations. In the appendix, a number of tips and relevant informations are catalogued for the use of the practising organic chemist.

The author has fulfilled his stated intentions admirably. By successfully applying the various steps involved in the interpretation of the mass spectra to common types of compounds, the author has brought out the role of mass spectrometry in the elucidation of the structure of organic compounds. Some of the other books in mass spectrometry are complementary material for this book.

The book is strongly recommended for use by all students of organic chemistry who are interested in using mass spectrometry as a physical probe. This publication is timely, useful and important in a field which is generating an ever-increasing amount of new information on the unimolecular reactions of gaseous organic ions.

K. GANESH DAS

BERYLLIUM TECHNOLOGY, METALLURGICAL SOCIETY CONFERENCE SERIES (Gordon & Breach Science Publishers, New York), 1966. Vol. 1: Pp. xii +678. Price $ 35.00 (cloth); $ 19.00 (paper). Vol. 2: Pp. xii+679-1255. Price $ 35.00 (cloth); $ 19.00 (paper)

The proceedings of the second international conference on beryllium technology have been published in two volumes; the first volume deals mainly with physical properties of beryllium and the second with the fabrication processes employed in the manufacture of various beryllium components.

The importance of beryllium purification has been stressed, since purity is a significant factor influencing the mechanical properties of the metal. Methods have been suggested for obtaining high purity metal and how the trace impurities affect the CRSS for basal slip. Promising beryllium-based alloy systems have been studied, and beryllium-aluminium alloys have been found encouraging from strength/weight ratio as well as improved ductility points of view.

Some fundamental studies on the deformation characteristics of beryllium have been reported, which are of considerable interest. Particular mention may be made of the study on the ductile-brittle transition in beryllium. In this, a new theory based on the thermally activated cross slip of screw dislocation from basal plane to pyramidal or prismatic planes has been proposed. Many high temperature physical processes, such as creep, grain boundary migration, etc., are closely related to diffusion and hence diffusion studies have been made to determine both self-diffusion and impurity diffusion in beryllium.

Bendability of beryllium sheets is governed by the texture it possesses and there are a few papers on textures and associated properties. Methods of forming beryllium at room temperature under high pressure have been discussed. This is equivalent to using high temperature which results in additional modes of deformation.

The liquid quenching technique has been successfully employed to obtain a composite material containing beryllium particles surrounded by soft aluminium matrix. This material exhibits marked bend ductility subsequent to heat treatment. In pure beryllium, splat cooling technique has been employed to obtain fine grain size which is required for improved mechanical properties. On the whole, Vol. 1 is of considerable value to physical metallurgists who would like to pursue any research problems in beryllium and also to applied metallurgists who would like to employ beryllium as a structural material.

The articles in Vol. 2 deal with successful development of shaping and fabrication processes as well as design and application of beryllium structures. There are two articles reviewing the progress and advances made in these fields, since the 1961 international conference on beryllium metallurgy held in London. Both the reviews are comprehensive and well written, but there is considerable overlapping of material covered by them. This is probably inevitable in such a large collection of papers.

The increasing importance of beryllium from a purely nuclear material to a promising structural material with an attractive strength/weight ratio is well reflected in the volume. Of the nineteen papers in this volume, only one deals with nuclear application of the metal; the rest are devoted to beryllium technology as related to aerospace and other non-nuclear applications. Extrusion, forging, casting, gas pressure consolidation, brazing, braze-welding, soldering and solid state bonding are some of the fabrication processes covered in the papers. The optimum conditions for successfully carrying out these operations and the influence of process variables on the properties of the ultimate product are discussed. A large number of examples of beryllium components developed by these processes for space vehicles and missile hardware are documented together with excellent photographs of the structural parts. Even though many details of the processes involved are not discussed, presumably to safeguard the business interests of the author's organizations, the articles do succeed in conveying that " the problem of forming beryllium was often greatly exaggerated and could be eased if the designer took cognizance of the inherent deficiencies of metal which has unique virtues in several directions ".

M. K. ASUNDI

MACHINE DEVICES AND INSTRUMENTATION, edited by Nicholas P. Chirones (McGraw-Hill Book Co., New York), 1966. Pp. vii+359. Price $ 10.00

This book is an excellent compilation of mechanisms and devices required for a wide variety of functions in instruments, automatic machines and control systems. Mechanical, electro-mechanical, hydraulic, thermal, pneumatic, photo-electric and optical devices have been illustrated in great detail, as also their applications for instruments and machine control.

In Chapters 1 and 2 of the book are given arrangements for feeding, sorting, transporting, automatic stop and safety mechanisms. In Chapter 3 are presented modern linkage design techniques. Design curves and formulae are given for gear mechanisms, slider cranks, four-bar power linkages, Geneva mechanisms, cardioid drives and power cams. In Chapters 4 and 5, mechanical components and special design devices for automatic control are given. Chapter 6 illustrates electrical components and various types of transducers used for automatic control, while switching mechanisms and magnetic devices are illustrated in Chapter 7. In Chapter 8, descriptions and illustrations of thermo, pyro and photo actuated devices are given. Chapters 9 and 10 deal with pneumatic and hydraulic control applications. In Chapter 11 are presented various measuring and recording devices for flow, liquid level and weighing systems.

The book provides useful information not easily available elsewhere. It will be extremely useful as a reference work for machine design engineers and those connected with design in instrumentation, automatic machinery and hardware for control systems. The editor is to be warmly commended for describing in a systematic way the machine devices and gadgetry required for automatic machinery and instrumentation design.

A. RAMACHANDRAN

ENGINEERING MATERIALS AND THEIR TESTING: PART II — NON-FERROUS METALS AND THEIR ALLOYS by D. S. Naidu (Asia Publishing House, Bombay), 1966. Pp. xvi+275. Price Rs 18.00

The following aspects of non-ferrous metallurgy are dealt with in this book: extraction, casting, metallography, heat treatment, chemical analysis, corrosion testing, mechanical working and testing. Considering the vast volume of information available on each of the above topics, it is to be expected that full justice cannot be done to the subject if one condenses them into a mere 275 pages. The treatment is skin deep, depth being sacrificed for breadth. Theoretical discussions have been completely omitted. There is not a single figure of an equipment or a phase diagram or a photo-micrograph in the entire book. The chemical analysis described is usually of the conventional type. Instrumental methods of analysis could have been incorporated to make the reader aware of the increasing applications of these to metallurgical analysis.

The list of minerals given on pages xiv and xv is repeated on pages 2 and 3. The list itself contains a few errors, e.g. composition of zircon is given as ZrO_2 on page xv; $CuFeS_2$ has been mentioned once as copper pyrite and again as chalcopyrite (p. xiv). Similar is the case with ZnS on the same page. On page 79, para 3, 'paste of magnesium powder . . . .' should be 'paste of magnesium oxide power . . . .'. The symbols of elements have been given in capital letters at the top of some pages, e.g. AL instead of Al from pages 17 to 33. On the whole, however, the language of the book is simple and precise. The author has given some useful data about alloys. Any practising engineer will find this useful to select an alloy for a particular purpose. As far as the students of engineering are concerned, it is doubtful whether the book will serve any purpose beyond the introductory stage.

G. S. TENDOLKAR

CLAYS AND CLAY MINERALS, PROCEEDINGS OF THE FOURTEENTH NATIONAL CONFERENCE, BERKELEY, CALIFORNIA (Pergamon Press Ltd, London), 1966. Pp. vi+443. Price £7

The book incorporates 35 papers presented at the fourteenth national conference organized by the Clay Minerals Society, USA. It is divided into four parts, the first three comprising papers presented at three symposia and the fourth, on miscellaneous topics.

The basic structures of most of the clay minerals were formulated in the 1930's. However, recently sophisticated techniques have made possible slight modifications and refinements to the structure of clay minerals. The quantitative analysis of clay minerals has also received considerable attention through the application of techniques such as X-ray diffraction, thermal and infrared analyses. However, the problem is far from resolved because there is a large variability in the results obtained by these techniques. There is also a need for an acceptable nomenclature for clay minerals and in 1965 the International Mineralogical Association prepared a report, after assessing the opinions of clay mineralogists from different countries. These are some of the important aspects discussed in 8 papers in the symposium on 'Structure and Quantitative Analysis'.

The interaction of clay plates in a clay-water system, the use of electrical conductance measurements, and thermal decomposition of ammonium and cobalt-clay complexes are some of the topics dealt with in the symposium on 'Surface Reactivity'.

Clay mineral identification and genesis have always attracted mineralogists' attention and this is evident in 7 papers presented in the symposium on 'Genesis and Synthesis of Clays'.

The fourth part consists mainly of new data on the fabric analysis, low frequency $(OH)^-$ motions and orientation of adsorbed organic molecules on the clay surface. These are mainly based on the application of electron microscopy, neutron inelastic scattering spectra and infrared spectroscopy.

The Clay Minerals Society has maintained a high standard of papers, as in the preceding publications. The book is especially recommended to those engaged in research on clays and associated silicate minerals.

V. S. RAMACHANDRAN

HOW TO WRITE A RESEARCH PAPER by Ralph Berry (Pergamon Press Ltd, Oxford), 1966. Pp. 92. Price 8*s*. 6*d*. net

The main aim of this little do-it-yourself manual is to help students taking a first degree course, and those preparing for a Diploma in Art and Design, or a Diploma in Education in UK in the writing of a research paper, thesis or a dissertation. The book sets out clearly and concisely the main points involved in the preparation of papers under the following 6 chapters: (1) The choice of the subject; (2) Preparing a bibliography; (3) Taking notes; (4) Composing the paper; (5) The final version; and (6) Some errors to avoid. A specimen paper is considered in a chapter. Though the author states in the introduction that the manual is not concerned with purely scientific and technical areas of research, it provides useful aids to research workers in science and technology in the preparation of a research paper.

The first chapter begins with a discussion of ways and means of selecting a topic for research and the choice of a title, and provides practical hints on the use of library resources. In the second chapter, primary, secondary and published and unpublished sources of information are discussed and suggestions as to how to go about in preparing bibliography are given. The system of note-taking and types of notes are discussed in Chapter 3. Useful hints are provided in the preparation of notes. The

various steps in the composition of a paper, viz. making a skeleton outline and writing of a rough draft and improving it are set out in the next chapter. The preparation of the final version of the paper, with particular reference to format, documentation, additional matter to be included, etc., is detailed in the fifth chapter. A model paper, set out in accordance with the principles laid down in the earlier chapters, comprises the sixth chapter. The final chapter recapitulates the main types of errors in student writing under four heads: Purpose and conclusion; Documentation; Shape and flow; and Presentation.

The book should be a welcome addition to the libraries of colleges imparting instruction in humanities at the postgraduate level.

A. KRISHNAMURTHI

A REFERENCE BOOK OF ENGLISH WORDS AND PHRASES FOR FOREIGN SCIENCE STUDENTS by R. F. Price (Pergamon Press Ltd, Oxford), 1966. Pp. 171. Price 21s. net

The author of this excellent reference book was Lecturer in Science Method at the University College of Science Education, Cape Coast, Ghana, and is, therefore, most competent to write such a book. During his work, the author must have been keenly aware of the difficulties experienced by science students in non-English-speaking countries in finding correct non-technical words and phrases to describe scientific events and tests. As the author has stated in the foreword, this reference book should be used as an aid when reading books on science, making notes, or when describing experiments. The book is not intended to teach science or scientific terms, but the non-technical English words and phrases which are necessary to describe and explain things and events scientifically. The book should prove useful even in India, as the standard of technical writing in the English language in the country has been steadily declining in recent years. A reference book like this should provide the basis for a course of lectures for students of science and technology at the undergraduate and graduate levels. It should prove particularly useful during practical instruction in the laboratory.

The introductory section 'Instructions to the Readers' should be carefully read, as this provides the key how the book could and should be used. The two main parts of the book are: (i) Science as observation and experiment, and (ii) Science as description and explanation. The first part which forms the bulk of the book (pp. 3-137), has 3 chapters (Qualities of things; Relations; and Actions). These chapters comprise illustrations, with captions covering objects whose qualities are shape, texture, colour, relations (quantities, spatial and temporal relationships) and actions. The second part is a short one (pp. 141-167) comprising five chapters (Facts, concepts and problems; Scientific method; The particular, the general and comparisons; Causation; and Classification) concerned with explanation, and short discussions of illustrative passages from standard elementary texts are included. The reader's attention is specially drawn to the exhaustive and useful index at the end of the book in which the page on which a particular use of a word is demonstrated is given in bold type.

The author and the publishers must be congratulated for the large number of excellent and simple black and white line drawings, as well as colour illustrations provided in the book. The book is highly recommended to students of science and technology, and it should definitely find a place in the libraries of schools, colleges and technical institutions.

A. KRISHNAMURTHI

PUBLICATIONS RECEIVED

NONLINEAR ELECTRON-WAVE INTERACTION PHENOMENA by Joseph E. Rowe (Academic Press Inc., New York), 1965. Pp. xiv+591

OPTICAL INTERFEROMETRY by M. Francon (Academic Press Inc., New York), 1966. Pp. xi +307. Price $ 13.50

FOUNDRY DIRECTORY, 1966 (The Institute of Indian Foundrymen, Calcutta), 1966. Pp. xciv+728. Price Rs 65.00

ADVANCES IN HETEROCYCLIC CHEMISTRY: Vol. 7, edited by A. R. Katritzky & A. J. Boulton (Academic Press Inc., New York), 1967. Pp. xiv +511. Price $ 22.00

ELECTRIC POWER IN ASIA AND THE FAR EAST, 1964 (United Nations, New York), 1966. Pp. viii +106. Price $ 2.00 or Rs 12.00

INDUSTRIAL CHEMISTRY by R. C. Bhatacharjee (Inter University Press, Delhi), 1967. Pp. 216. Price Rs 15.00

INVESTIGATIONS IN THE FIELD OF ORGANOLEAD CHEMISTRY by L. C. Willemsens & G. J. N. Van der Kerk (International Lead Zinc Research Organization Inc., New York), 1965. Pp. 135

STRUCTURAL CONCRETE by K. F. Antia (The New Book Co. Pvt. Ltd, Bombay), 1967. Pp. 572. Price Rs 35.00

HANDBOOK OF ULTRAVIOLET AND VISIBLE ABSORPTION SPECTRA OF ORGANIC COMPOUNDS by Kenzo Hirayama (Plenum Press, Data Division, New York), 1967. Pp. 642. Price $ 40.00

STUDIES IN PETROCHEMICALS (United Nations, New York), 1966. Vol. 1: Pp. xi+568. Vol. 2: Pp. viii+569-1078. Price $ 25.00

EXPERIMENTAL TECHNIQUES IN PHYSICAL METALLURGY by V. T. Cherepin & A. K. Mallik (Asia Publishing House, Bombay), 1967. Pp. xi+428. Price Rs 30.00

COMPUTER PROGRAMMING AND COMPUTER SYSTEMS by Anthony Hassitt (Academic Press Inc., New York), 1967. Pp. x+374. Price $ 10.75

ORGANIC REACTIONS: Vol. 15, edited by Arthur C. Cope (John Wiley & Sons, New York), 1967. Pp. vii+607. Price $ 18.00

NOTES & NEWS

A new bridge for measuring small mutual inductances

A bridge circuit capable of measuring very small mutual inductances has been designed at the Institute for Basic Standards, National Bureau of Standards, Washington. The bridge is of transformer-ratio-arm type, having a ratio of 10 to 1, and can compare mutual inductors through 5 orders of magnitudes from 0·1 μH. to 1 mH., at a frequency of 1592 Hz. The simplified circuit is shown in Fig. 1.

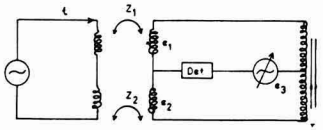

Fig. 1 — Simplified inductance bridge circuit

During the operation, the ratio

$$\frac{Z_1}{Z_2} = \frac{e_1}{e_2}$$

is compared with the 10 to 1 voltage ratio of an inductive voltage divider, which may be calibrated by a modification of the capacitance-ratio method. The bridge balance is accomplished by the adjustment of e_3 which is an adjustable voltage source. The detector consists of a tunable amplifier and a tuned high impedance preamplifier, coupled to the bridge through an impedance matching transformer. At the smallest level of inductance measured, the sensitivity is 1 part in 10^7 and the sensitivity improves at larger values of inductance such that 100 μH. can be compared with 1 mH. with a sensitivity of a few parts in 10^8 [*J. Res. natn. Bur. Stand.*, **70C** (1966), 221].

New test for blood proteins

Currently, serum proteins are identified by coupling them to coloured dyes and then they are quantitatively estimated with a densitometer by the amount of light that the dyed protein absorbs. Various correction factors have to be applied to the densitometer reading, depending upon the dye used. A more simple and rapid method for quantitatively determining the albumin and globulin contents of the blood serum free from this difficulty has been developed [*Chem. Engng News*, **45** (No. 12) (1967), 24]. The method combines electrophoresis and fluorometry and is most suited for clinical testing. 8-Anilinonaphthalene-1-sulphonic acid, a colourless stain used in the method, is itself nonfluorescent but when associated with a nonpolar site of a protein, the combination becomes fluorescent.

The steps in the method are similar to those now used. A fraction of a drop of the serum being tested is placed on an electrophoretic support medium at *p*H 8·8. Thin films of agarose gel, a very pure form of agar, are used in this method. Zone electrophoresis is carried out in the usual manner. When separation of the proteins is complete, the agarose strip is dipped in a perchloric acid-formaldehyde mixture (to denature, or fix the proteins), and then in a 0·003 per cent solution of the stain. This is followed by a series of rinses to remove the excess stain. The stained strip is scanned with a motorized attachment to a Turner model 111 fluorometer. Fluorescence of the different protein zones shows up on a linear recorder. The percentage of each protein fraction is calculated by measuring the area under each peak.

The method has many advantages over the procedures now used. It allows direct quantitative readings on the fluorometer, because no correction factors need be applied. It is 10 times more sensitive than the densitometer method. For example, the protein content of 0·003 microlitre of normal blood serum can be measured quantitatively. The agarose used has many advantages over the other support materials, such as paper and cellulose. It is transparent and almost colourless. The strip thickness can be controlled. It is easy to dissolve away the agarose support if specific fractions of the separated proteins are needed for further investigation.

High lysine and tryptophan corn

A high lysine and tryptophan corn bred from mutant opaque-2 gene, known as opaque-2 or 0-2 corn, was the topic of discussion at the High Lysine Corn Conference at Purdue University, USA. Although discovered 30 years ago, its potentiality as a source of quality protein has not been investigated till recently. 0-2 corn was found to contain over 60 per cent more lysine and 66 per cent more tryptophan than regular hybrid corn. Both these amino acids are usually low in vegetable proteins which necessitates supplementation of these amino acids from other sources to vegetable proteins for full body growth and tissue synthesis.

Nutritional studies carried out with non-ruminants (since protein requirements of ruminants are not based much on quality) gave promising results. The milling characteristics of this new corn were quite satisfactory. The amount of starch present was less though there was no change in its properties. Higher yield of germ oil and steep water, and an improved quality glutin feed were noted. Fermentation characteristics were satisfactory although the alcohol yield was reduced.

The new corn is available only in limited quantities at present, and the problems of identifying and separating 0-2 corn from regular varities have to be overcome for large-scale production of this corn. When these problems are solved man can look forward to having a new 0-2 corn strain which can be of nutritional value equal to that of milk [*Chemurg. Dig.*, **24** (No. 5) (1966), 4].

Micro tissue culture assay

A simple, rapid and reproducible micro tissue culture assay in the BS-C-1 (Ceropithecus monkey kidney) cell line has been developed for the titration and

neutralization of measles virus [*Can. J. Microbiol.*, **13** (1967), 313].

Serial dilutions of virus (or serum) are made with spiral loops in disposable microplates and 8×10^3 BS-C-1 cells suspended in 0·05 ml. of medium 199 with 2 per cent fetal bovine serum are added to each dilution. After the addition of 0·1 ml. of sterile mineral oil to each microculture, the plates are covered with a plexiglass sheet and placed in a fumidified incubator (37°C.) under a constant pressure of 5 per cent CO_2 for 5 days. Micro tissue cultures are examined with the aid of an inverted microscope for viral cytopathic changes on the fourth and fifth day.

The chief advantage of the micro assay is the replacement of the conventional pipettes with spiral loops or microdilutors for the serial dilutions of reagents. This method is not only considerably faster but also eliminates the complicated procedure of changing outgrowth medium to maintenance medium. The 2 per cent fetal bovine serum which is added to the medium 199 not only promotes the outgrowth of the BS-C-1 cells but is sufficient for their 5-day maintenance in microplates.

The ' one-step ' micro assay can be applied to the *in vitro* potency testing of various live, attenuated measles vaccines, as well as to the antibody titration of human and animal sera following vaccination with either live or inactivated measles vaccines. The test may also be used for measuring the antimeasles potency to human gamma globulines.

Summer school in optical engineering and technology

A summer school in optical engineering and technology, sponsored by the University Grants Commission, was held at the Applied Physics Department of the Andhra University, Waltair, during 6-24 June 1967. Twenty-one candidates attended the school. They included personnel from private industry, Defence Science Laboratory (Ministry of Defence) and Central Scientific Instruments Laboratory (CSIR), besides college lecturers and advanced students. Prof. V. Ramakrishna Rao of the Department of Applied Physics, Andhra University, was the Director of the summer school.

Dr C. S. Rao (Andhra Scientific Co., Masulipatam) delivered four lectures on the design, development and testing of optical instruments. Dr M. V. R. K. Murty (Bhabha Atomic Research Centre, Bombay) dealt with ' Interferometry applied to testing of optics ', and Dr M. De (University College of Technology, Calcutta) covered, in the course of seven lectures, the principles and applications of holography and optical image evaluation. Prof. V. Ramakrishna Rao spoke on thin film technology, optical glass and electro-optical methods for detecting radiation. Colorimetry and design of illumination systems were also among the topics dealt with.

Quiet sun symposium

The results of research carried out during the 1964-65 period, designated as the International Quiet Sun Years, were discussed in a symposium on IQSY during the annual meeting of the National Academy of Sciences, USA.

Scientists from 71 countries participated in research programmes connected with IQSY. IQSY proved a good sequel to the International Geophysical Year and one of its main achievements, according to Martin A. Pomerantz, Chairman, US Committee for conducting IQSY programmes, was " the solidification of earth-sun research into a new discipline — solar-terrestrial physics ".

The various researches showed that space is a caldron of forces, particles and plasmas interacting in a variety of complex processes unknown even ten years back. On the sun itself the lower corona is a web of fine magnetic ropes, tightly looped from one sunspot to another. Herbert Friedman (Naval Research Laboratory, USA) theorized that thin magnetically trapped threads of plasma are ' pinched ', resulting in rapid increases in temperature and density to produce X-rays. Electrons can be accelerated in local active regions to energies of more than 10,000 eV. producing additional X-rays.

Friedman's study also indicated that thermal content of solar wind, a constantly blowing stream of hot ionized particles, is a primary source of the evolution of active regions in the solar chromosphere and corona. The energy of the solar wind, capable of meeting all the energy requirements of solar flares, is often stored in a coronal ' helmet ' structure. As its instability grows, the magnetic lines snap near the base of the helmet's spike, and a jet of high energy solar cosmic ray particles is launched into space.

Kenneth G. McCracken (Southwest Centre for Advanced Studies) emphasized that solar wind is the most important single feature which determines the behaviour of the interplanatory magnetic field which again dominates the behaviour of cosmic radiation. The earth's magnetic field hollows out a cavity in the solar wind, which sweeps back the outermost lines of force on the dark side of the earth in a comet-like tail that extends past the orbit of the moon.

Other interesting discussions on the physics of interplanetary space, magnetosphere, bulge in the outer atmosphere of the earth, etc., also took place.

UGC seminar on chemisorption and catalysis

A seminar on chemisorption and catalysis, sponsored by the University Grants Commission, was held under the auspices of Madras University during 27-31 March 1967 in the Chemistry Department of the Loyola College, Madras. Because of the scientific and industrial importance of the subject the seminar was well attended. The participants numbering 45 represented various university, technological and industrial research laboratories: Indian Institute of Petroleum, Dehra Dun; Central Fuel Research Institute, Jealgora; Fertilizer Corporation of India, Sindri; Bhabha Atomic Research Centre, Bombay; Laxminarayana Institute of Technology, Nagpur; Indian Institute of Technology, Kharagpur; Regional Research Laboratory, Hyderabad; Indian Institute of Science, Bangalore; Christian Medical College, Vellore; Neyveli

Lignite Corporation, Neyveli; Indian Institute of Technology, Madras; Chemistry Department, University of Madras; and Loyola College, Madras. The seminar was inaugurated by Dr A. L. Mudaliar, Vice-Chancellor of Madras University.

Thirty-four research papers were presented in 11 technical sessions, each session comprising about 3 papers and each paper taking about 20 min. for reading and 10 min. for discussion. The kinetics of hydrogen adsorption on ZnO, ferrochrome, Ni-Al_2O_3 and MoS_2 were examined in the light of Elovich equation in order to characterize the surface heterogeneity of these catalysts. The study of the interaction of CO with metal powders over a wide temperature range seemed to point to the occurrence of physical and chemical adsorption and the formation of surface carbonyl complexes. The reactions of uranium oxide, both as a solid and as a gaseous substrate, were explained in terms of the variable valency of uranium ions and crystal structure of the oxide, and a possible application of this explanation to other gas-solid systems was indicated. As an indication of the comprehensive nature of the adsorption phenomenon, a paper was presented on the sorption of water vapour on collagens prepared in different ways with a view to bringing out their reactive centres.

Several papers were concerned with the use of alumina and modified aluminas for the dehydration of alcohols and terpene ketones, isomerization, both skeletal and double bond, of cyclic olefins, and dehydrogenation of monoterpenes. The influence of added alkali, acids and organic bases on the acidity of alumina and hence on the rate and course of the reaction is fairly understood. However, a new insight brought out in the seminar is the effect of the added materials on the size and shape of the alumina pores and the role of these in certain reactions which cannot be explained on the basis of acidity variations. Also, the *p*H of the medium was reported to influence considerably the structure and texture of MgO catalysts. A detailed study of the dehydration of various alcohols over thoria furnished definite evidence for the presence in it of basic sites.

The mechanism of dehydration and dehydrogenation of alcohols over chromia and chromia-alumina was discussed in terms of their semiconductor characteristics according to Wolkenstein's model. The dehydrogenation of 3-carene on these catalysts was given a new interpretation in terms of the oxidation states of chromium ions, determined by chemical methods and electrical conductance measurements. The dehydrogenation of cyclohexane to benzene over Ni-MgO was sought to be correlated with its adsorption properties. A new interpretation of the dehydration and dehydrogenation of cyclohexanol over NiO and doped NiO was offered in the light of electrical conductivity measurements.

The role of iron both as a promoter and inhibitor in the oxidation of petroleum hydrocarbons in gas and liquid phases was indicated and the mechanism involved discussed. The oxidation of methanol and ethanol over vanadium oxide catalysts from the viewpoint of kinetic rate equations was reported. Also, the temperature characteristics of the oxidation of H_2S over active carbon catalysts were described and accounted for. The kinetics of the dehydrocyclization of normal paraffins over Cr_2O_3-Al_2O_3, of the dehydrogenation of cyclohexane over nickel-zinc oxide catalyst and the catalytic hydrogenation of benzene to cyclohexane were presented from a developmental viewpoint. Some kinetic problems encountered in the design of fixed bed catalytic reactors were outlined and their solution discussed in terms of known theoretical principles.

The reduction to a very small percentage of CO in the gases used for ammonia synthesis is of technical importance. One paper described a mixed catalyst of ferric, cupric, manganous and silver oxides on kieselguhr and the optimum conditions for the oxidation over it by air at rather low temperatures of CO in a mixture of CO and H_2. Another paper dealt with the correct percentage of Cr_2O_3 in chromia ferric oxide commercial catalyst to prevent its crumbling during the reaction. The dependence of the activity of this catalyst on diffusion phenomena was discussed in the third paper. The effect of operating variables such as temperature, pressure, space velocity, etc., on the actual performance of an imported catalyst in the oxidation of CO was described in the fourth paper.

To indicate the wide range of operation of the catalytic processes, the mechanism of the proton catalysed isomerization of monoterpenes in liquid phase and the catalytic role of simple molecules and ions in the halogenation of aromatic compounds, including the application of isotopic kinetic effect, were discussed.

Every day there was a general lecture on one of the following topics by an eminent chemist: chemisorption, heterogeneous catalytic reactions, catalysis in the synthesis of macromolecules, liquid phase catalysed isomerization of monoterpenes, and enzyme catalysis. Mr J. Simon, Technical Adviser of EID Parry Ltd, spoke on "Catalytic processes in ammonia plant and their operating problems", indicating the sort of problems which could be taken up for study in a research laboratory. Mr R. V. Ramani, Director of Mettur Chemical & Industrial Corporation, gave a talk on "Problems of research in heavy inorganic chemicals" and a practical way of bringing about a closer contact between chemists in research and in industry.

The main recommendations made at the conclusion of an informal discussion held on the fourth day were: (i) some of the industrial catalysts and reactions needing further study to be taken up for investigation in research laboratories; (ii) a closer contact to be fostered between research laboratories and chemical industry, such as fertilizer plants, petroleum refineries, petrochemical plants, etc.; (iii) a mimeographed news service to be started through CSIR if possible between various laboratories working in the field of catalysis for mutual benefit and for preventing duplication of research; and (iv) desirability of having a seminar every two years on chemisorption and catalysis, and circulating the papers some time before the meeting, so that more of the time could be spent on discussion than on presentation of the papers. — L. M. YEDDANAPALLI, *Loyola College, Madras*

Calcified Tissue Research

This new quarterly periodical started by Springer-Verlag from the beginning of 1967 is to serve as a medium for the publication of results of researches on the structure and function of bone and other mineralized systems in living organisms. It will also publish reports and reviews on subjects like connective tissues and cells, ion metabolism and transport, hormones, nutrition, ultrastructure and molecular biology. The annual subscription for the periodical is $ 15.00 or £ 5.50 or DM 60.

Shri K. D. Sharma

Shri Kapil Dev Sharma has been appointed Director, Central Glass & Ceramic Research Institute, Calcutta. Shri Sharma (born July 1920), after graduation from the Panjab University, obtained the B.Sc. (Glass Tech.) degree, standing first in order of merit from the Banaras Hindu University. He worked in the glass industry for about a year and in 1945 proceeded to UK for higher studies as a Government of India scholar. He carried out research work at Sheffield University under Prof. W. E. S. Turner, F.R.S., and Prof. H. Moore and obtained the M.Sc. (Tech.) degree. Thereafter, he worked in the glass plants of Rockware Glass Ltd, Greenford, UK, and Karhula Lasitehdas, Finland. He joined the Central Glass & Ceramic Research Institute, Calcutta, as Scientific Officer in September 1948 and was associated with the planning and development of the institute from almost the beginning. During 1953-54, he worked at the Glass Section of the National Bureau of Standards, USA, as a guest worker. He visited USSR in 1959 as a member of the Government of India Expert Team for the optical and ophthalmic glass project and went to USA and UK in 1962 as alternate leader of the NPC Study Team on Glass Industry.

Shri Sharma has been Deputy Director of the institute since 23 August 1960 and Scientist-in-Charge since 22 August 1966. His outstanding contribution has been the development and production of optical glass, a strategic defence material, for the first time in India. Some other important projects with which he has been associated include the development of foam glass, radiation shielding windows for nuclear reactors, glass moulds, study of fuel efficiency in glass melting furnaces, glass raw materials, productivity, etc.

Shri Sharma is a Fellow of the Society of Glass Technology, UK, Member of the International Commission on Glass, Honorary Secretary of the Indian Ceramic Society, and Chairman of ISI Sectional Committee for Glassware.

National Physical Laboratory, New Delhi

The annual report of the laboratory for the year 1965-66 surveys the major research and developmental activities of the various divisions during the year. The standardization, calibration and testing work conducted is also recorded. The quarterly publication *NPL Technical Bulletin* was started from January 1966. For the first time, the laboratory observed an Open Day during the year. Plans were finalized to establish a Materials Group in the laboratory. At the get-together between industries and research laboratories organized during the year, the laboratory was allotted 11 projects for work on priority basis, top priority having been given to projects on (1) carbon composition resistors, and (2) setting up of comprehensive testing and standardization facilities for electronic components.

Notable among the research activities of the laboratory are those relating to (1) propagation of sound waves in granular media; (2) chemical kinetics of reactive systems; (3) noise surveys; (4) acoustical requirements of auditoria; (5) clinical thermometers; (6) thermal conductivity measurements; (7) battery separators; (8) rheological properties of carbon mixes; (9) projector carbons; (10) platinum resistance thermometers; (11) daylight studies; (12) thin films; (13) single crystals; and (14) International Quiet Sun Year programme. It has been shown that sand and soil can be used effectively for sound insulation. A steady state, radial heat flow method for thermal conductivity determination for large aggregates and large conductivity blocks, such as those of heavy concrete has been developed. Studies on battery separators have shown that the efficiency of a separator is better if the calculated resistance is low and the product of porosity function and surface area is high. The performance of the separators has been found to bear no relationship with permeability or mean pore size. A new method developed for the manufacture of projector carbons enables simultaneous extrusion of the shell and the core mix.

In the field of radio and space physics, a new and comprehensive approach to ion kinetics was made in the light of the recent space measurements of solar XUV radiation, ion composition and electron density profiles and new laboratory measurements of rate coefficients. A new multi-frequency analysis technique was developed for the determination of the F region contribution to normal cosmic noise absorption. A technique for estimating the F region effects on sudden cosmic noise absorption events was developed. An atmospheric model for solar minimum condition was developed using the satellite drag measurements. In this model, the height variation of the concentration of atmospheric constituents like N_2, O_2, O, He and H together with atmospheric scale height, mean molecular mass and atmospheric temperature in the height range 100-700 km. are given for diurnal minimum, average and maximum conditions.

In separate appendices, the progress achieved in respect of 84 research projects and 32 developmental projects and 8 projects relating to standardization work is described. A separate appendix is devoted to pilot plant work on projector carbons and electronic components.

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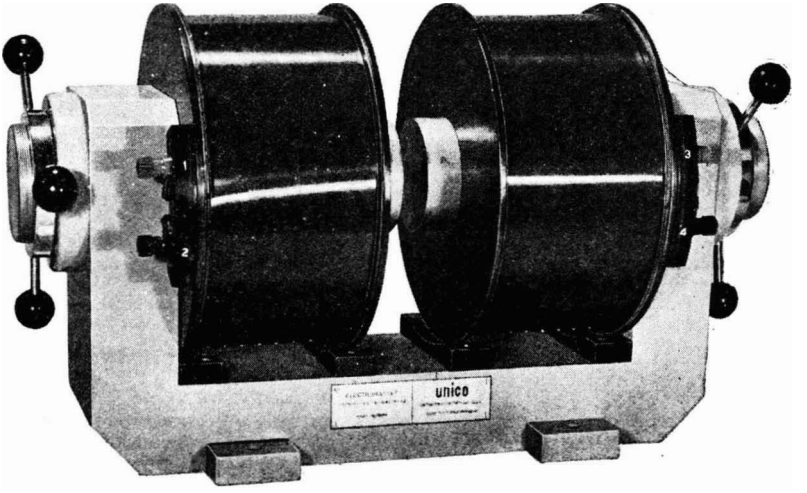

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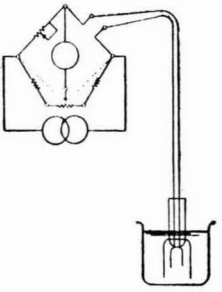

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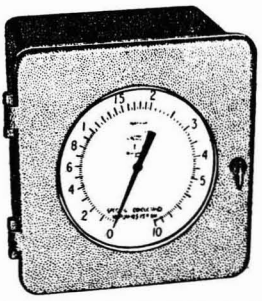

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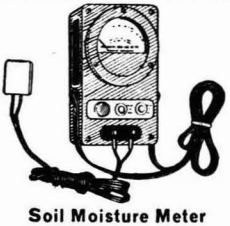

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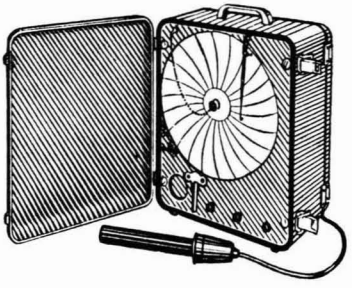

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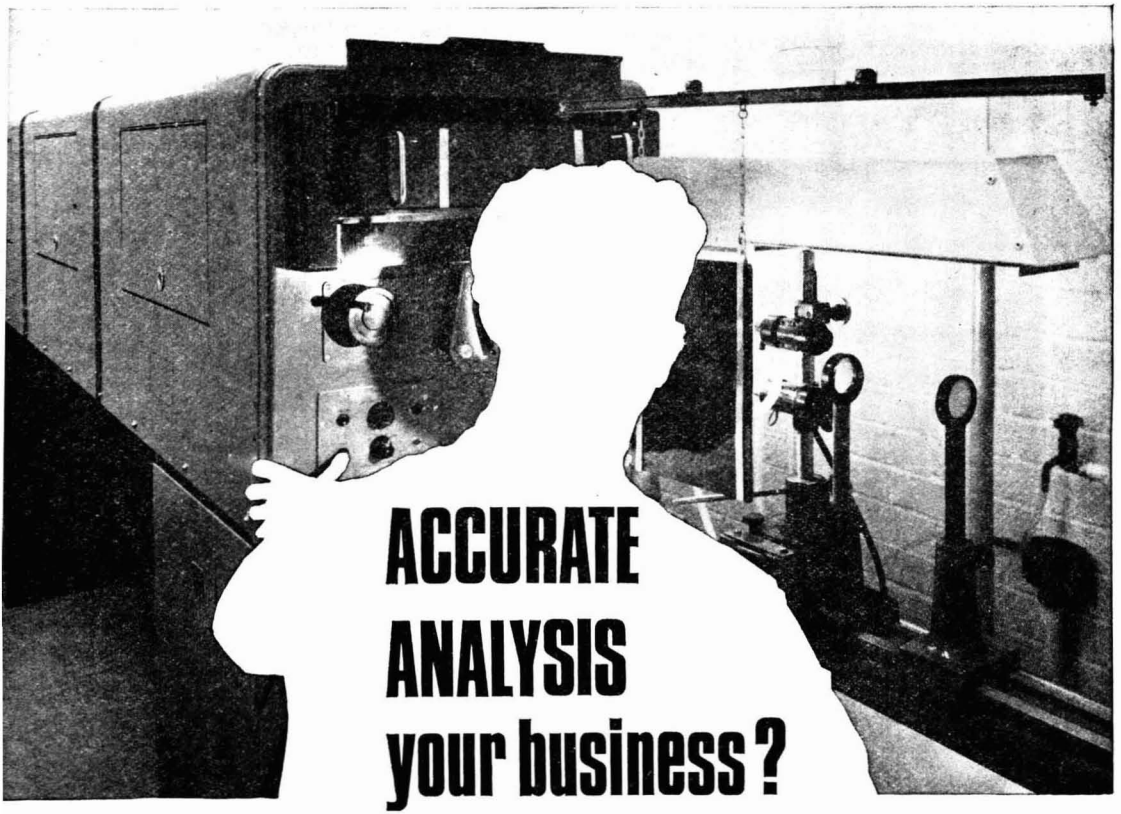

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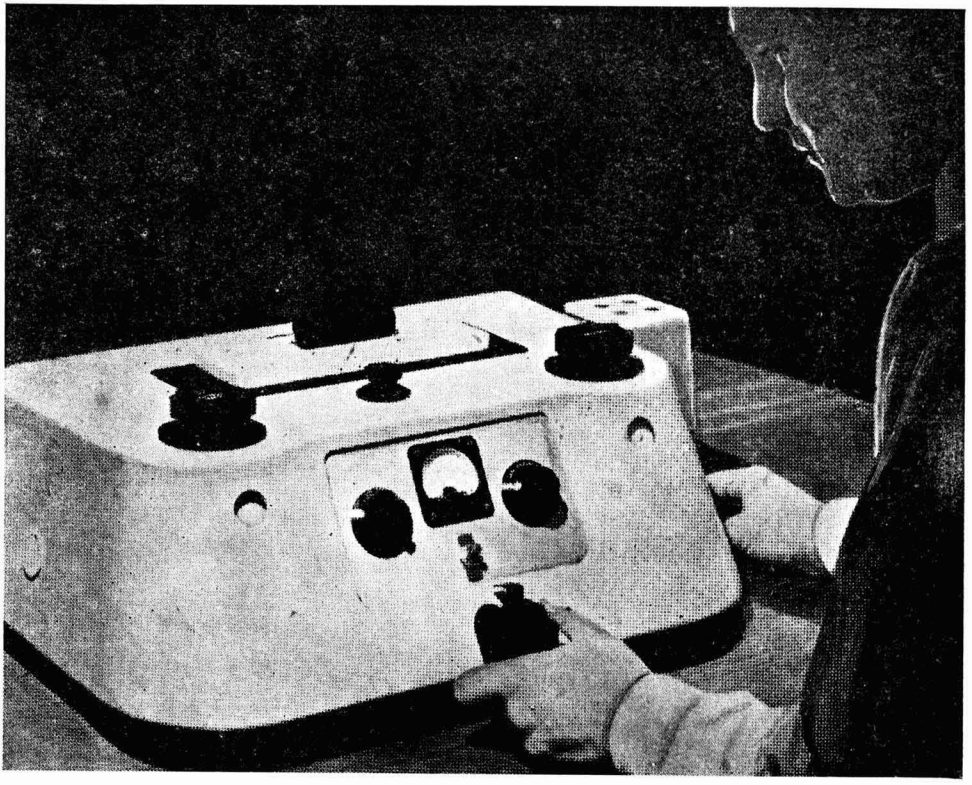

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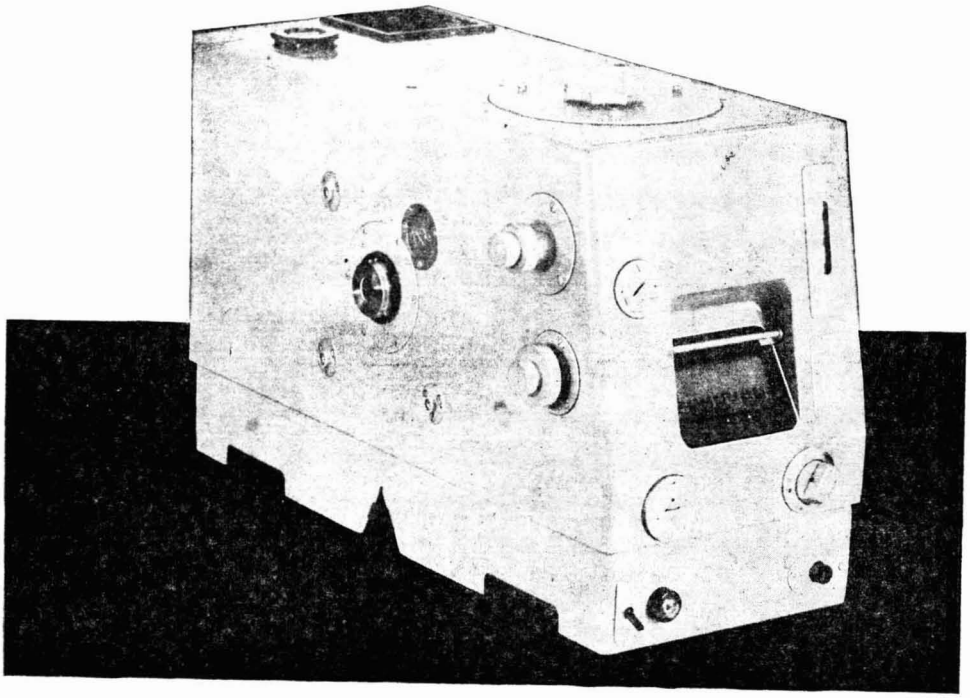

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