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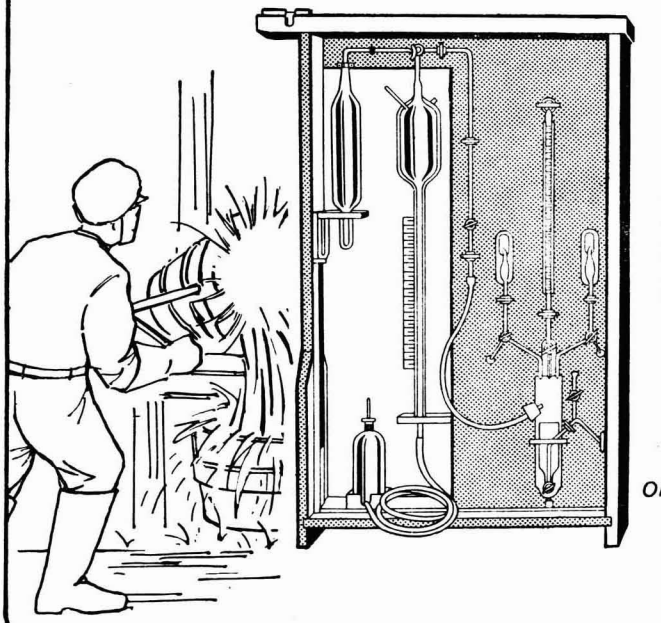

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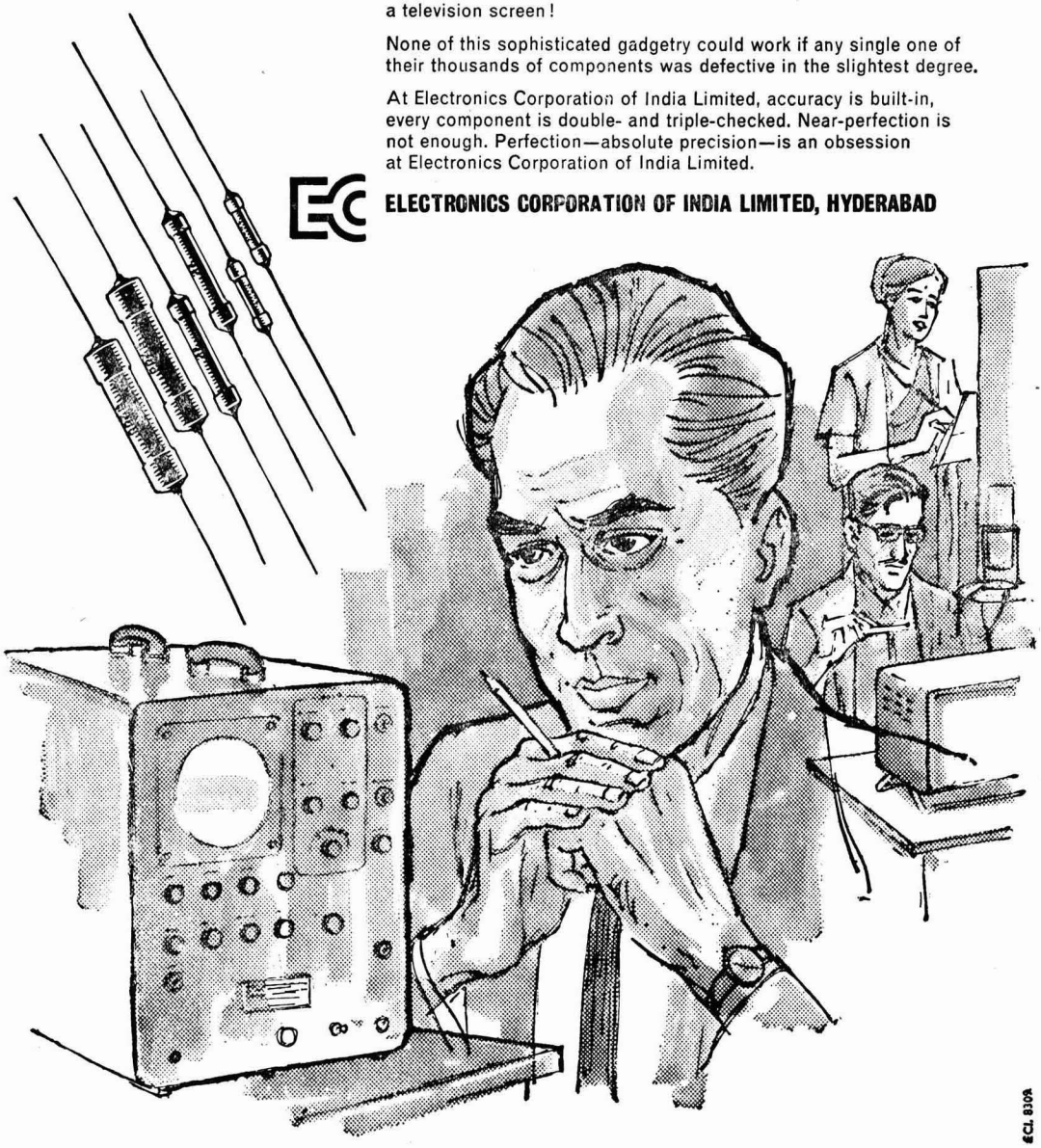

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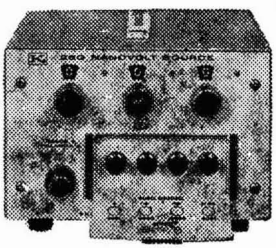

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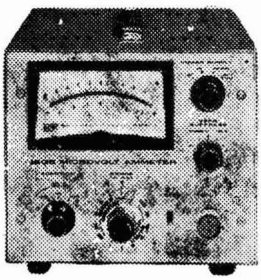

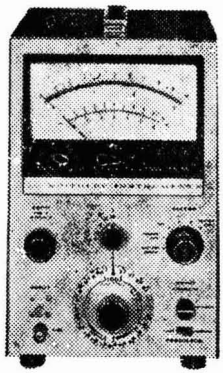

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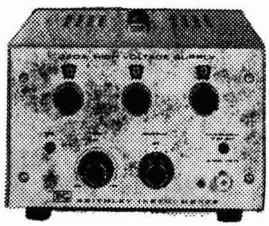

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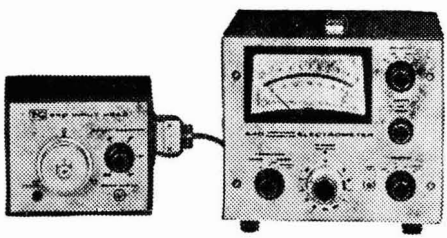

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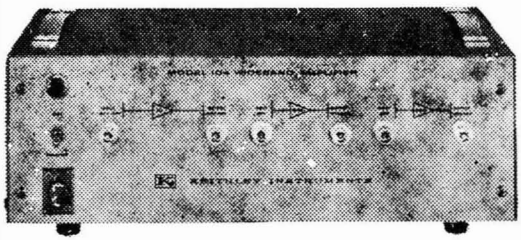

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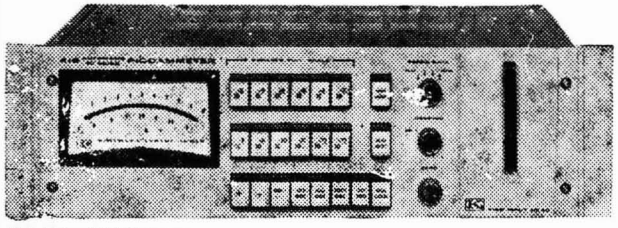

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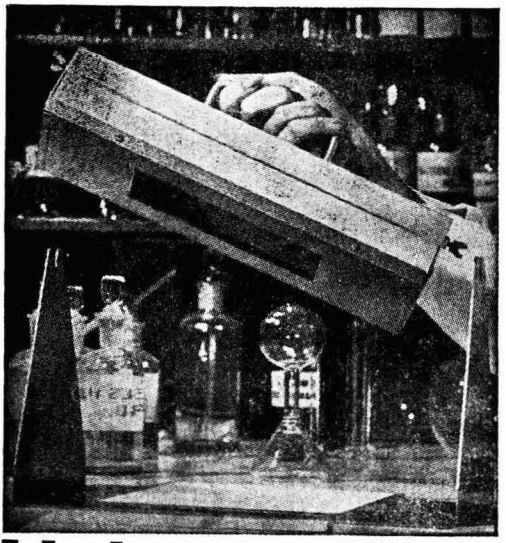

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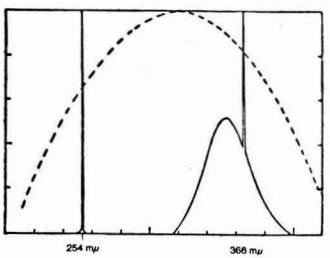

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SUPPLEMENT

to

Glossary of Indian Medicinal Plants

by

R. N. Chopra, I. C. Chopra & B. S. Varma

In the year 1956, the Council of Scientific & Industrial Research, New Delhi published a Glossary of Indian Medicinal Plants with a view to presenting concise information regarding their properties, uses and important constituents. Over 2600 species, belonging to about 1350 plant genera, have been dealt with. The information is given under the botanical names of the plants, which are arranged in their alphabetical sequence; trade and vernacular names are also mentioned. The Glossary gives distribution of the plants, diseases for which the particular plant is used, and the active principles. Adequate literature references to the sources of information are also provided. The book ends with two comprehensive indexes: one pertaining to the vernacular and trade names, and the other to the chemical constituents.

In order to bring the Glossary up to date, this Supplement has been brought out. It follows the style of the Glossary and covers all relevant information published during the period 1955-64. The Supplement provides additional information on over 700 species already mentioned in the Glossary, and includes about 380 new species. Indexes covering additional vernacular and trade names and chemical constituents have been provided. The Supplement, like the original Glossary, will be useful not only to the practitioners of indigenous system of medicine, but also to all others who are interested in drugs of vegetable origin and common bazaar medicines.

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Current Topics

Man Round the Moon

THE circumlunar flight of Apollo-8 with three Americans aboard and their safe return to the earth is an important landmark in the annals of human achievement. It is a tribute to both the courage of the three pioneering astronauts and to the sophisticated technology and amazing precision of many aspects of the flight schedule. Apollo-8 mission was a necessary prelude to the realization of the ultimate goal of landing a man on the moon. Its two major aims were: (i) to prove the capability of the craft's command module (CM) and the service module (SM), and (ii) to see whether the crew can effectively operate at lunar distances, including the ability to establish two-way effective communication between the spacemen and the ground control. The mission was an endurance test for the astronauts and the instrumentation and control. Though planned on a step-by-step 'commit point' basis, every phase of the mission was successfully carried out exactly as planned in advance.

The Apollo-8 space flight has created a number of space firsts. The Saturn-V launching vehicle used was 363 ft tall, developed a combined thrust of 7·5 million lb at liftoff — the highest for any spacecraft till now. It was the first space vehicle in which man escaped out of the grip of the earth's gravity, and experienced for the first time the feeble gravity and magnetic field of another heavenly body, viz the moon. The astronauts experienced the highest speed of about 25,000 miles/hr — more than the escape-velocity of 24,200 miles/hr for the earth — and re-entry velocity of 24,700 miles/hr. For communicating with a manned spacecraft at lunar distance, it used for the first time a 4-dish, unified, S-band, high-gain antenna swinging out of the SM.

Apollo-8 was launched from the Kennedy Space Centre in Florida, USA, at 6.21 p.m. IST on 21 December 1968, at an azimuth of 72° and it was first put into an earth orbit at a height of 103 miles. During the second orbit, the Saturn-V third stage engine was re-started, giving the craft the boost necessary to attain the escape-velocity of the earth. Then the CM and SM separated from the third stage and began free-coasting into the trackless void in interplanetary space and headed for the moon for the next 66 hr. Initially, the craft was decelerated due to the pull of the earth's gravity and finally reached the critical boundary, where the influence of terrestrial gravity practically ceases and that of moon first begins to exert. This historic moment came exactly at 1.59 a.m. on 24 December 1968 when the Apollo-8 was at about 203,000 miles from the earth and about 30,000 miles from the moon. The flight was smooth and went on with perfect precision — even a scheduled midcourse correction was not necessary. Once in the gravity grip of the moon the craft began speeding up slowly again and when it reached a speed of 5720 miles/hr at 3.28 p.m. on 24 December 1968, the astronauts successfully put themselves into a moon orbit. This was achieved by firing the 20,500 lb thrust service propulsion engine (in a brief burst of 4 min 6 sec) to slow the craft to allow it to be pulled by the moon into an elliptical orbit, which was finally circularized at a height of 69 miles above the moon surface. The moon orbiting manoeuvre was carried out when the craft was in the 'communications shadow' of the moon for about 36 min. The spacemen circled the moon at 3640 miles/hr for 10 orbital periods of about 2 hr each, during which period the crew conducted navigational and photographic investigations. After 10 lunar orbits, the service propulsion engine was again fired (for 3 min 26 sec) to enable the craft to attain a speed of 6060 miles/hr, more than that adequate to escape from the gravity of the moon, putting it into a direct trans-earth journey. In the course of their 58 hr homeward journey, the spacecraft was at first slowed down to about 3000 miles/hr and then, when it re-entered the edge of the earth's gravitational field, picked up speed again to reach an ultimate 24,700 miles/hr, just before re-entry into the earth's atmosphere. Another critical and skilful manoeuvre which had to be conducted before their final descent to the mother planet was to hit a 2° re-entry corridor — a 26-mile diameter slot of space at an altitude of 400,000 ft. To maintain a constant build-up after 6 days of weightlessness, the astronauts made a 'skip' from about 180,000 ft back to 210,000 ft before nosing over into their final descent. The heat shield successfully withstood the searing temperature developed (about 3300°C) as the capsule fell through the dense layers of the atmosphere and the craft gently splashed in the Pacific at 9.21 p.m. on 27 December 1968, exactly according to the time-table.

Six TV transmissions were made by the astronauts during the period they were on their way to the moon, in orbit round the moon and on their way back to the earth. In those telecasts, observers on the earth could clearly see more than four-fifths of cloud-wrapped earth as a bright object. The astronauts described the oceans as royal blue and the land mass as dark brown. The TV pictures of the moon showed clearly the horizon and the brightly lit moon surface showed some craters with dark centres. The astronauts took both still and motion pictures of the earth in its entirety as it looks from deep space and of the moon from distances as close as 70 miles and of the possible

landing sites on the moon. The present photographs excel over earlier ones taken by automatic cameras in fixed positions in that the astronauts had the freedom to choose ' targets of opportunity ' and aim and to adjust them at desired targets, such as the still undetected features. In the Apollo-8 programme, ground network coupled with on-board navigational techniques is expected to sharpen the accuracy of lunar orbit determinations and check the extent of the likely ' wobble ' in the spacecraft's orbit introduced by mass concentrations below the lunar surface. The data and experience gained from Apollo-8 mission provide first-hand information for an astronaut landing on the moon.

While pragmatists may be critical of the wisdom of spending extravagant sums of money on such apparently unproductive projects, man's insatiable quest to challenge and conquer the unknown will continue despite occasional setbacks. The important outcome of the Apollo-8 mission is the assurance that the present technology is adequate for man to venture into deep space and come safely back to the earth.

High Polymer Symposium

GAUTAM RAY

Department of Physical Chemistry
Indian Association for the Cultivation of Science, Jadavpur, Calcutta 32

IN the fields of chemistry and physics, the area of polymer science has a unique fascination, and growing interest has been discernible for some time among the scientific workers in India. An informal conference of delegates from the active polymer research centres of India was held at the Regional Engineering College, Kurukshetra University, Kurukshetra, during 29 September - 2 October 1968. The meeting was sponsored by the Department of Applied Science, Kurukshetra University, financially supported by the University Grants Commission and directed by Dr H. L. Bhatnagar, Professor of Chemistry, Regional Engineering College, Kurukshetra University. An excellent opportunity was thus provided to the workers in the field to know each other's work. The papers presented were as varied as they were interesting in their contents. A résumé of the technical proceedings of the symposium is given below.

D. K. Sarkar [Indian Association for the Cultivation of Science (IACS), Calcutta] discussed the highly interesting phenomenon of co-solvency, ie the solubilization of a polymer in suitable mixtures of two or more non-solvents, viz polystyrene in *n*-hexane-diethyl oxalate, polyethylene in acetone-chlorinated hydrocarbon-carbon disulphide at room temperature, polymethyl methacrylate in carbon tetrachloride-methanol/ethanol, etc. An optimum composition with maximum solvent power has been found in each case by studying the osmotic μ-value, Huggin's constant, intrinsic viscosity or dissymmetry coefficient as a function of composition. D. Mangaraj [Harcourt Butler Technological Institute (HBTI), Kanpur] reported a decrease in the glass temperatures of styrene-acrylate copolymers with increasing acrylate content. According to his data, chain geometry of the comonomers and chain stiffness appear to determine the glass temperatures of the copolymers. M. Singh (Panjabi University, Patiala) gave the values of K and a in the Mark-Houwink equation for butyl rubber fractions at 37°C in toluene, *p*-xylene, tetralin, decalin, chlorobenzene and bromobenzene. The values of the above parameters for G-R-S fractions in toluene, chlorobenzene, *o*-chlorotoluene and cyclohexane, in the temperature range 21-50°C, were reported by R. S. Oberoi (Regional Engineering College, Kurukshetra). R. P. Rastogi (Gorakhpur University) gave an invited lecture on rocket fuels. His associate, S. K. Baijal, discussed the synthesis of cross-linked polymers having O—B—O linkages, and a copolymer of triallyl

borane and methyl methacrylate, all of which were unusually stable. These boron-based polymers, for a time, found use as rocket fuels in the technologically advanced countries.

Papers by the delegates from the Shri Ram Institute for Industrial Research, Delhi, covered subjects of industrial importance. S. K. Gupta discussed how incorporation of isophthalate in the polymer chain stabilizes the chlorendate polyesters. It is to be noted also that a γ-irradiation dose of 18·0 Mrads converts these unsaturated polyesters from *trans* to *cis* form. R. S. Parikh reported that the moisture regain of cotton fabrics, cross-linked with various resins, increases initially to a maximum and then decreases to a minimum with increase in the degree of cross-linking under all swelling conditions. R. K. Bhatnagar reported that in the case of plasticizers synthesizable from castor oil, the ratio of molecular weight to the number of polar groups present in the molecule seems to provide a good correlation between the relative plasticization efficiency and the chemical constitution of the plasticizers. N. B. Sattur reported a study on methylol fatty alkyl monocarbamates, mainly from the point of view of their possible use as internal lubricants.

I. K. Varma (Indian Institute of Technology, Delhi) described her work with W. I. Bengough on the dehydrochlorination of polyvinyl chloride in

solution in an atmosphere of nitrogen over the temperature range 178-243°C using benzophenone, tributyl phosphate, ethyl benzoate, dioctylphthalate, dichloronaphthalene and benzyl alcohol as solvents. The apparent activation energies are in the range 22-30 kcal/mole. The rate is fast in benzophenone and tributyl phosphate, depends on the first power of polymer concentration, and has no systematic dependence on the degree of polymerization. I. S. Gur and H. L. Bhatnagar (Kurukshetra University) reported that the thermal degradation of G-R-S in dilute solutions of chlorobenzene, *m*-xylene and decalin in the temperature range 120-50°C proceeds by a random chain scission process. The rate determining step appears to be the rupture of the hydroperoxide links. A theoretical treatment of light scattering by inhomogeneous spherical particles was also presented by S. B. Mal and H. L. Bhatnagar.

In an invited lecture, V.D. Gupta [Indian Institute of Technology (IIT), Kanpur] talked fascinatingly on the application of the random walk problem to the configurational studies of high polymers. R. V. Subramanian (HBTI, Kanpur) reviewed the field of polymerization of α-olefins with Ziegler-type catalysts. Invited lecture by K. J. Balakrishna (Defence Research and Development Laboratory, Gwalior) was on the plastics utilization in the defence industries. U. S. Nandi (IACS, Calcutta) talked on the peculiar cooperative phenomenon often observed when the functional groups are in the monomeric units of the polymer chains. His own observation of stronger antioxidant properties of polymeric phenols in comparison with ordinary phenols also intrigued the delegates.

Workers associated with IACS, Calcutta, formed the largest single group at the conference, and presented papers on various aspects of polymer chemistry. A. K. Chaudhuri reported the kinetics of bulk copolymerization of styrene-alkyl methacrylates and examined the applicability of Arlman's theory of penultimate unit effect on the variation of the ϕ-factor with monomer feed composition. The redox dye, 2,6-dichlorophenol indophenol, both in its acid and base forms, was described by B. M. Mandal to be a powerful retarder of free radical polymerization of styrene and methylmethacrylate. A probable scheme, postulating the intermediates in the retardation process, has been advanced on the basis of the retardation kinetic study. The potential of these inhibitor dyes as preservatives for vinyl monomers was pointed out. B. Sen reported the achievement of phenanthrene-carbon tetrachloride sensitized vinyl polymerization for the first time. The behaviour of fluoro-chemicals can be unpredictable, and this was evidenced from the chain transfer data of some fluoroalcohols [$H-(CF_2-CF_2)_n-CH_2OH$, where $n = 1, 2$ and 3] in the catalysed polymerizations of styrene, methylmethacrylate, vinyl acetate and acrylonitrile at 60°C, as reported by I. Kar. The transfer constants depend on the reactivity as well as on the polarity of polymeric radicals. The results have been interpreted in terms of polar transition state theory. G. Ray reported from an end group study that the heterogeneous sodium bisulphite/MMA polymerization system in the aqueous medium produces branched molecules at ordinary temperatures when the conversion is high. It has been shown that the tool of end group analysis can be used to probe the growth history of branched molecules in free radical polymerization. T. Sengupta reported that halogens in the presence of a redox component, viz urea, thiourea, amide, cyanoguanidin, etc, are efficient initiators of vinyl polymerization.

G. C. Bhadury and U. S. Nandi (IACS, Calcutta), in their report on the kinetic study of styrene and methylmethacrylate in the presence of glycols as chain transfer agents, keeping the polymerization medium homogeneous by the use of a second solvent, observed a decrease in the degree of polymerization (DP) with increasing glycol concentration, but there appears to be a critical concentration region above which DP increases monotonically. They thought that at higher glycol concentrations the solvent action becomes poorer and extended structures of the growing polymer chains collapse into compact coils, resulting in a reduced rate of termination and so a rise in DP.

The symposium also heard reports from the fast expanding frontiers of biopolymer science. B. P. Gothoskar (Cancer Research Institute, Bombay) discussed the inhibitory action of acridines in the biological activities *in vitro* of DNA, viz (i) self-replication, and (ii) RNA synthesis. D. Balasubramanian (IIT, Kanpur) on the basis of a light scattering study reported that poly-L-alanine in pure dichloroacetic acid has essentially the shape of the α-helix. Protonation of amide residues does not, therefore, appear to be responsible for the helix-coil transition of polypeptides in nonpolar solvents, effected by the addition of strong organic acids.

The discussions of the papers were spirited. Delegates exchanged their views freely and frankly. Perceptible was an uneasy awareness of the new frontiers opening up in the fields of polymer science, which Indian workers are unable to explore due to lack of sufficient facilities. But the delegates showed a strong will not to lag behind for long in the highly competitive field of polymer research. The opinion was thus expressed in the meeting that a symposium and/or a summer school on high polymers should be held at least once in a year. A move was also initiated to form a scientific body, which will be called 'The Polymer Association of India'. The Government of India should also do its part to popularize polymer research in India. Ready availability of the monomers from indigenous sources will no doubt encourage many laboratories to undertake investigations on polymer science and technology.

Acknowledgement

The author wishes to express his grateful thanks to Prof S. R. Palit for his valuable scrutiny of the manuscript.

Kinetics & Mechanisms of Polymerization with Ziegler-type Catalysts*

R. V. SUBRAMANIAN
Department of Chemistry, H.B. Technological Institute, Kanpur

THE discovery of the Ziegler catalysts[1] for the low pressure polymerization of ethylene to high density polyethylene quickly followed by their application by Natta *et al*[2] for the stereoregular polymerization of α-olefins initiated a revolution in polymer chemistry. The explosive developments in research and technology that followed this initial discovery have been described extensively[3,4]. The number of mechanisms postulated are exceeded only by the variety of catalyst combinations tried to obtain Ziegler-type catalysts. More systematic studies have been undertaken in recent years which permit a clearer understanding of the factors that control the activity and specificity of these complex catalysts. It is, therefore, useful in this necessarily short review to touch upon only a few aspects of the kinetics and mechanisms of polymerization with Ziegler-type catalysts, drawing on our results of investigation[5,6] in this area as much as possible. These relate to the polymerization of styrene by lithium isoamyl-$TiCl_4$ and chromium acetylacetonate-aluminium triethyl combinations.

These heterogeneous olefin polymerization catalysts are generally formed by the reaction of a reducible transition metal compound from groups IV to VII with a metal alkyl or metal hydride of the elements of groups I to III of the periodic table. The most efficient combinations involve aluminium alkyls with titanium halides. Homogeneous catalysts are formed when organic ligands instead of halides are attached to the transition metal as in titanium dicyclopentadienyl dichloride or chromium acetylacetonate.

The initial reaction of the metal alkyl with the transition metal compound, eg $TiCl_4$, is one of alkylation followed by reduction. The reduced titanium halide is precipitated. Depending upon the nature and ratio of metal alkyl concentration to that of titanium, further reduction or complex formation can occur. For example, we can write the following series of reactions for $TiCl_4$ and a lithium alkyl (LiR):

$$TiCl_4 + RLi \rightarrow RTiCl_3 + LiCl$$
$$RTiCl_3 \rightarrow TiCl_3 + R$$
$$TiCl_4 + nRLi \rightarrow RnTiCl_{4-n} + nLiCl$$
$$TiCl_3 + RLi \rightarrow TiCl_3RLi$$
$$TiCl_3 + RLi \rightarrow RTiCl_2 + LiCl$$
$$TiCl_3.RLi + RLi \rightarrow TiCl_3(RLi)_2$$
$$RTiCl_2 + RLi \rightarrow R_2TiCl + LiCl$$

The course of reduction of vanadium, chromium and other transition metal compounds probably follows the same general pattern described for the titanium compounds. However, there have been no systematic studies of the catalyst forming reactions with these metals as with titanium.

Once the insoluble precipitate of a reduced transition metal halide is formed, further reactions, ie alkylation, complex formation, etc, would be heterogeneous, occurring on the surface of the precipitate. Hence, the analysis of the total catalyst precipitate, bulk and surface together, to determine the extent of reduction may not be relevant in understanding the nature of the catalyst and mechanism of polymerization which depend on the electronic state of the transition metal on the surface of the catalyst. Unfortunately, there are no measurements of valency confined only to the surface of the catalyst precipitate. It is, therefore, difficult to explain, in a fundamental way, the variation of polymerization characteristics with the mole ratio of the catalyst components, though it is an important variable in Ziegler-type polymerizations and can control the yield and molecular weight of a polymer, rate of polymerization and also the degree of stereoregularity of a polymer (Table 1). There can be little doubt, however, that the influence of this ratio is connected with the catalyst structure and the valency state of the transition metal forming the catalyst.

For different catalyst systems, different maxima are obtained for the same monomer. Thus, potassium alkyls with titanium tetrachloride give maximum conversion of ethylene at ratios of K: Ti between 2 and 5 (ref 12), whereas lithium *n*-hexyl shows a maximum conversion at a Li: Ti ratio of 2·2 (ref 13). Vinyl carbazole gives a maximum conversion with the lithium butyl-titanium tetrachloride catalyst at a Li: Ti ratio of 1·8 (ref 14), whereas with the same catalyst, maximum activity for styrene is observed at Li: Ti ratios between 1·75 and 2·25 (ref 15). On the other hand, using lithium isoamyl-titanium tetrachloride, the maximum rate of styrene polymerization is observed at a Li: Ti ratio of 2 (ref 5). The observation of maximum activity at different ratios of the same catalyst components for different monomers (Table 1) suggests the formation of different catalyst sites specific for polymerization of different monomers.

The presence of different sites having different activity and stereospecificity is evident from the significant changes brought about in the rate of polymerization and especially in the degree of stereo-

TABLE 1 — INFLUENCE OF THE MOLE RATIO, Al: Ti, ON THE YIELD AND STEREOREGULARITY FOR DIFFERENT MONOMERS

Monomer	Al : Ti for maximum yield	Al : Ti for maximum stereo-regularity
Ethylene[7]	2·5	—
Propylene[8]	2·0	3·0
1-Butene[9]	2·0	2·0
4-Methyl-1-pentene[10]	1·2-2·0	1
Styrene[11]	2-3	3

*Paper presented at the Symposium on High Polymers held during September 1968, at the Department of Chemistry, Kurukshetra University, Kurukshetra.

regularity of the polymer by the addition of certain compounds having strongly complexing ligand atoms. Ziegler *et al*[16], for example, found that the addition of electron donor molecules, ie Lewis bases such as amines, increased the stereospecificity of some catalysts and also converted certain non-stereospecific catalysts into stereospecific ones. Since then a wide variety of oxygen, sulphur and nitrogen-containing substances as well as unsaturated compounds have been tested out on Ziegler-type catalysts. Since electron donor molecules interact strongly with aluminium alkyls, Boor[17] investigated the effect of such molecules on catalysts formed from zinc diethyl and titanium trichloride. Zinc diethyl does not complex with electron donors and so the effect of the latter on the Ziegler catalyst surface could be studied without its being masked by any strong interaction with the metal alkyl component. It was found that there is an initial sharp decrease in catalyst activity at ratios of $(C_2H_5)_3N$: Ti of about 0·1. The yield of polymer decreased from 80 to 40%, but simultaneously the stereoregularity of the polypropylene increased from 65 to 90%. On increasing the amine: Ti ratio further to 0·5-3·0, the catalyst becomes more active than in the absence of triethylamine and there is a further small increase of the stereoregularity of the polymer from 90 to 93%. Evidently, both the removal of active sites and the activation of catalyst sites occurred. Boor found no detectable heat change for the reaction of the donor molecules involving 'site removal'. This was consistent with the fact that the number of active catalytic sites on the surface was small[18]. However, there is a large and detectable heat of interaction resulting in site activation. This indicates that the donor molecules, in this process, are adsorbed throughout the catalyst surface.

There is evidence that such modification of the activity of the catalyst results sometimes from molecules formed in side reactions of Ziegler catalyst components. We have found, for example, that *trans*-stilbene is formed in the reaction mixture during the polymerization of styrene by lithium isoamyl-titanium tetrachloride[5]. It was proposed that this had the effect of reducing the stereoregularity and molecular weight of the polymer formed with this catalyst and was confirmed by the study of the effect of added stilbene on the performance of an $Al(C_2H_5)_3$-$TiCl_4$ catalyst. There was considerable acceleration in rate, while simultaneously a reduction in the crystalline fraction of the polymer was also observed (Table 2). The acceleration in rate may involve the effect of the stilbene adsorbed in the proximity of the active site on the polarity of the polymer-metal bond.

The remarkable effect of the electron donor molecules recommends their consideration as integral components of Ziegler catalysts which were hitherto described as consisting of only an organometallic in combination with a transition metal compound. For example, though monoalkyl dihalides of aluminium are ineffective with $TiCl_3$ as catalysts for α-olefins, $TiCl_3$-$Al(C_2H_5)Cl_2$ with hexamethyl phosphoric triamide (HPT) added becomes a good catalyst of high stereoregularity (97·2%)[19,20]. The activity of the donor molecule increases with increasing basicity in the series $(C_4H_9)_3N > HPT \approx (C_4H_9)_3P > (C_4H_9)_2O > (C_4H_9)_2S > (C_4H_9)I$.

Among the other variables that determine the activity and stereospecificity of the Ziegler-type catalysts, the change of the transition metal and the metal alkyl components is the most important. Tables 3-5 summarize some illustrative examples.

It is seen from Table 4 that the activity of the catalyst varies in reverse order to the stereoregularity. Similarly, the activity decreases in the order[23] $Al(C_2H_5)_3 > Al(C_2H_5)_2Cl > Al(C_2H_5)Cl_2$ with $TiCl_3$. $Al(C_2H_5)Cl_2$ acts as a catalyst only when electron

Table 2 — Effect of Added Stilbene on the Polymerization of Styrene (0·87 mole/litre) by $Al(C_2H_5)_3$ (0·06 mole/litre)-$TiCl_4$ (0·02 mole/litre) Catalyst in Benzene[5]

trans-Stilbene mole/litre	$Rp \times 10^6$ mole litre^{-1} sec^{-1}	Crystalline polystyrene %	Molecular weight $\times 10^{-5}$
0	3·6	32	2·8
0·1	5·7	14	2·0
0·2	5·7	12	0·81

Table 3 — Influence of Transition Metals on the Stereoregularity of Polypropylene[21]

Transition metal compound	Stereoregularity %
$TiCl_4$	48
$TiBr_4$	42
$TiCl_3$, α, γ	80-92
$TiCl_3$, β	40-50
$ZrCl_4$	55
VCl_3	73
VCl_4	48

Table 4 — Influence of the Structure of the Organometallic Compound $Al(C_2H_5)_2X$ in Combination with $TiCl_3$ on the Rate of Polymerization and Stereoregularity of Polypropylene[22]

X	Relative rates of polymerization	Stereo-regularity %
C_2H_5	100	83
F	30	83
Cl	33	93
Br	33	95
I	9	98

Table 5 — Stereospecificity of the Catalyst[4] in the Polymerization of Isoprene

Catalyst	Yield, %			
	cis-1, 4	*trans*-1, 4	1, 2	3, 4
$R_3Al + TiCl_4$ (Al: Ti>1)	96·1	0	—	3·9
$R_3Al + TiCl_4$ (Al: Ti<1)	—	95	—	5
$R_3Al + TiCl_4$	96	—	—	4
$R_3Al + \alpha$-$TiCl_3$	—	91	—	9
$R_3Al + TiCl_4$ + amine	100	—	—	—
$R_3Al + Ti(OR)_4$	—	100	—	—
$R_3Al + V(AcAc)_3$	—	—	—	90
$R_3Al + VCl_4$	—	99	—	—

donor molecules like HPT are added. However, $Al(C_2H_5)_2Cl$ is more stereospecific than $Al(C_2H_5)_3$. Similarly, with isobutyl aluminium the dependence of activity on the transition metal compound in the polymerization of propylene[24] can be expressed as $VCl_4 > VOCl_3 > TiCl_4 > ZrCl_4 > HfCl_4$. It has also been observed that the degree of stereospecificity of the catalyst generally decreases in the order $AlR_3 > BeR_2 > ZnR_2 > MgR_2 > LiR$ with variation of organometallic compound and in the order $TiCl_3 > TiCl_4 > Ti(OC_4H_9)_2Cl_2 > Ti(OC_4H_9)_3Cl > Ti(OC_4H_9)_4$ with variation of ligands attached to titanium. Even more illustrative of the specificity of the catalyst systems are the results of polymerization of isoprene (Table 5). Although these highly selective catalyst systems enable us to prepare polymers of well-defined structure, fundamental understanding is still lacking for the satisfactory explanation of all the observations.

It is possible for active sites on the heterogeneous catalyst surface to change with time (ie ageing) after preparation of the catalyst or to become clogged with precipitated polymer during polymerization. For example, polystyrene formed by lithium isoamyl-$TiCl_4$ in hexane is precipitated on the catalyst surface and catalytic activity quickly decreases[5]. However, when the polymerization is carried out in benzene, a good solvent for polystyrene, the polymer stays in solution leaving the catalyst with undiminished activity (Fig. 1).

The bulk of the evidence would thus indicate the presence of independent catalytic sites of varying activity and stereospecificity on the Ziegler-type catalyst surface. A controversy, however, arises about the roles of titanium and aluminium in the catalytic complex with respect to the active site of chain growth; nearly all possibilities in assigning the active site have found a place in the various theories postulated. There seems to be an agreement that the transition metal centre is the site where the α-olefin is complexed, prior to insertion into the growing polymer chain. Disagreement concerns whether the propagation stage involves a single metal centre or a bimetallic complex as centre. The various mechanisms have, therefore, been divided on this basis as 'bimetallic mechanisms' and 'monometallic mechanisms' and discussed in detail[4].

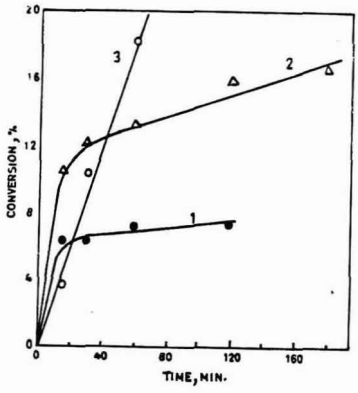


Fig. 1 — Percentage conversion versus time at 30°C [Mole ratio of Li: Ti = 1·5; styrene = 0·5766 mole/litre; $Li(i\text{-}C_5H_{11}) \times 10^3$ mole/litre in *n*-hexane (1) 5·03 and (2) 7·23 and in benzene (3) 1·94]

Natta[18] has vigorously advocated the bimetallic mechanism and in his view the polymer chain is always bound, at least partially, to the aluminium chemisorbed on the $TiCl_3$ surface, at which incomplete coordination of the titanium ions occurs. Polymerization proceeds by insertion of the monomer complexed with titanium into an alkyl bridge linking the titanium and aluminium atoms in the complex with three centre bonds. After partial ionic dissociation of the alkyl bridge of this complex, the complexed monomer is transferred to form a six-membered ring transition state. This structure collapses by insertion of the polarized monomer into the aluminium polymer bond (Chart 1).

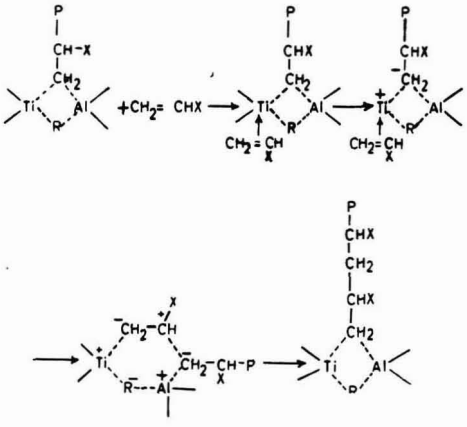


Chart 1

The concept of chain growth at the bridge head of a bimetallic electron deficient complex has been criticized by Ziegler[25] on the ground that addition of olefin in the Aufbau reaction occurred only with monomeric aluminium alkyls but not with the dimers in equilibrium with it. However, this would only imply that the olefin would not be complexed on the aluminium. Natta *et al*[26], from the presence in the polymer of end groups from aluminium alkyls of the catalyst, deduced that the site of chain growth was on aluminium. This conclusion has also been shown to be not quite valid by Karapinka and Carrick[27].

Karol and Carrick[28] have further studied the effect of variation of catalyst components on copolymerization of ethylene and propylene. The composition of the copolymers remained unchanged when the same transition metal compound was combined with various metal alkyls. On the other hand, it was strongly dependent on changes in the transition metal when the metal alkyl was kept constant. This indicated changes in the nature of the active site of the catalyst brought about by the changes in transition metal and provided strong support for chains growing on the transition metal. Analogous results were obtained by Danusso and Sianesi[29] for the copolymerization of styrene and *p*-methyl styrene

where identical reactivity ratios were observed with Et_3Al and $TiCl_3$ as well as with Et_2Be and $TiCl_3$.

These results are compatible with the monometallic mechanism of Cossee[30-32], Cossee and Arlman[33] and Arlman[34,35]. Cossee's elegant and detailed exposition using the most modern concepts of organometallic chemistry[36] throws reasonable insight into the polymerization of propylene on α-$TiCl_3$. Further, the mechanism developed is of much wider importance than for Ziegler polymerizations alone, since a variety of reactions like catalytic hydrogenation and the oxo reactions involve migration of an alkyl group or hydrogen in the catalytic complex. The essential features of the mechanism proposed by Cossee involve (A) the formation of active centre and (B) the process of chain growth as shown in Chart 2.

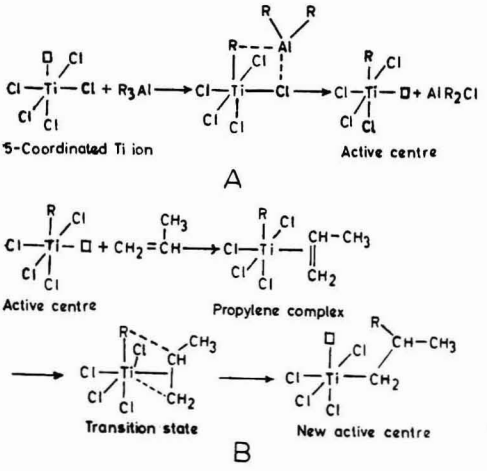
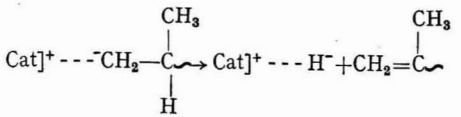


Chart 2

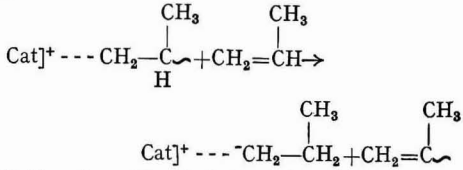
Here, the active centre is formed by alkylation of a penta-coordinate Ti^{3+} ion exposed by a chlorine vacancy on the surface through an exchange reaction with AlR_3. In the active centre thus obtained, the essentially octahedral surroundings are provided by the four chloride ions anchored in the interior of the solid lattice. The alkyl group is attached by a σ bond to the titanium ion. The vacant sixth position then receives the monomer to form a π-complex. No examples are known of olefins being bonded to transition metal ions in another fashion and, therefore, it is assumed that the α-olefin together with the active site forms a π-complex of the type described by Chatt and Duncanson[37]. Consideration of the ionic radii of the chloride ions, the van der Waals radii of the CH_2 part of an alkyl group and those of propene show that the double bond of propene can approach the central metal ion almost as closely as the halide ions. It is also seen that the ends of the alkyl group and the monomer to be inserted are brought together very closely in this complex. Chain growth then occurs by migration of the alkyl group to regenerate an octahedral vacancy and a new extended alkyl titanium bond. Thus, the proposed mechanism fully satisfies the requirement[38] that in the rate determining step, in which bonds are broken and new ones formed, the positions of the nuclei before and after the rearrangement should resemble each other as closely as possible.

Detailed studies on the dependence of molecular weight of the polymer formed have established four modes of chain breaking and regeneration of the active centre.

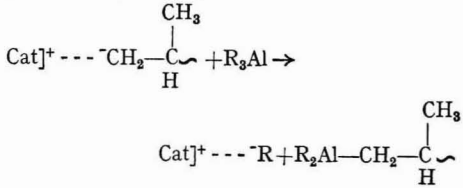
(i) Spontaneous dissociation of the polymer-catalyst bond via hydride transfer from the 2-position to yield an active catalyst-hydride bond and vinylidene terminated polymer chain



(ii) Transfer with the monomer



(iii) Transfer with alkyl aluminium



The spontaneous dissociation process yielding vinylidene end groups involves higher activation energy than chain growth and becomes relatively more important at higher temperatures[39]. Transfer with the aluminium alkyl seems to involve only the monomeric form present in equilibrium with the dimer, since the molecular weight has been found to be inversely proportional to the square root of the aluminium alkyl concentration[6]. Other metal alkyls like zinc diethyl are also capable of participating in the chain transfer process to bring about a lowering of the molecular weight[5]. In accordance with the monomeric nature of zinc alkyls, the chain transfer process is first order with respect to zinc alkyl concentration. Dependence of the molecular weight inversely on $[TiCl_4]^{\frac{1}{2}}$ yields another mode of chain limiting process dependent on $TiCl_3$ (ref 5).

Evidence is also available for a bimolecular termination mechanism when homogeneous Ziegler-type catalysts are used[6]. In the polymerization of styrene by $Al(C_2H_5)_3$-$Cr(AcAc)_3$, a homogeneous catalyst in benzene solution, the rate of polymerization is proportional to $[Cr(AcAc)_3]^{\frac{1}{2}}$. But when $Al(C_2H_5)_2Br$, instead of $Al(C_2H_5)_3$, is combined with chromium acetylacetonate, a heterogeneous catalyst results and the rate of polymerization is proportional to $[Cr(AcAc)_3]$. Similarly, Chien[40] observed that the rate of polymerization of ethylene was dependent on the square root of the concentration of the

homogeneous catalyst $Ti(C_5H_5)_2Cl_2$-$Al(CH_3)_3$. As is typical with a free radical polymerization, a bimolecular termination mechanism between active growing polymeric species is postulated to account for this observation. Representing the growing species by C^*, it follows that

$$2C^* \xrightarrow{k_t} \text{polymer}$$

and so

$$-\frac{d(C^*)}{dt} = 2k_t\,(C^*)^2 \qquad \ldots \qquad \ldots \qquad \ldots(1)$$

The growing species will be proportional to catalyst concentration, ie

$$\frac{d(C^*)}{dt} = k[\text{Cr(AcAc)}_3] \qquad \ldots \qquad \ldots \qquad \ldots(2)$$

Now if one makes the debatable assumption of a steady state for (C^*), then

$$2k_t(C^*)^2 = k[\text{Cr(AcAc)}_3]$$

and $$(C^*) = (k/2k_t)^{\frac{1}{2}}[\text{Cr(AcAc)}_3]^{\frac{1}{2}}$$

Since $R_p = k_p(C^*)(M)$, where k_p is the propagation rate constant,

$$R_p = k_p(k/k_t)^{\frac{1}{2}}[\text{Cr(AcAc)}_3]^{\frac{1}{2}}(M)$$

accounting for the observed dependence of R_p on $[\text{Cr(AcAc)}_3]^{\frac{1}{2}}$.

It is perhaps a just criticism to point out that a bimolecular termination and steady state assumption have been too readily thrust on the situation. But there seems to be no doubt that the homogeneous Ziegler-type catalysts do give rise to the observed square root dependence. It is also very reasonable to expect a bimolecular termination to occur when the growing species are in solution but not when they are bound on a catalyst surface. Chien[40], in the work cited above, actually found evidence for the occurrence of disproportionation in bimolecular termination between growing polyethylene species from the presence of 0·5—C=C group per polymer molecule.

Results of polymerization of isoprene with $Cr(AcAc)_3$-$Al(Et)_3$ further support the above arguments[6]. This catalyst, homogeneous at the dilute concentrations in which it was employed for the polymerization of styrene, became heterogeneous — as a fine black precipitate — at the high concentrations required for polymerization of isoprene. The rate of polymerization of isoprene is shown to be dependent on the first power of the concentration of $Cr(AcAc)_3$. The same catalyst, thus, yields different kinetic results under heterogeneous and homogeneous conditions.

Summary

The various factors that influence the kinetics, mechanism and stereospecificity of Ziegler-type catalysts are examined. The course of the catalyst forming reactions, the structure of the catalyst and the valency state of the transition metal forming the catalyst depend on the ratio of the concentration of the metal alkyl to that of the transition metal compound. The formation of independent catalyst sites on the surface of varying specific activity is strongly indicated, especially by the significant changes brought about by the addition of certain compounds having strongly complexing ligand atoms like triethylamine. The presence of such compounds seems to bring about both removal of some active sites and activation of other catalyst sites. Change in the transition metal and/or the metal alkyl component also effects selective modification of the stereospecificity and activity of the catalyst. Postulated mechanisms of chain growth involve both monometallic and bimetallic complexes as active centres. However, Cossee's elegant exposition of the growth mechanism using α-$TiCl_3$ in terms of an initial complexation of the olefin at the octahedral vacancy of a penta-coordinate alkylated titanium followed by alkyl group migration to regenerate an octahedral vacancy and a new extended alkyl titanium bond is not only theoretically sound and most attractive but also consistent with a large body of experimental evidence. Spontaneous dissociation of the polymer-catalyst bond, transfer with monomer and transfer with metal alkyl represent the general modes of chain breaking and regeneration of active centres. Evidence is also available for a bimolecular termination of active centres when homogeneous catalyst complexes are used.

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Non-steroidal Antifertility Agents Interfering with Different Phases of Reproduction in the Female

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STEPS in reproductive mechanism in the female which have shown susceptibility to chemical interference include: (1) *Ovulation*, (2) *Fertilization*, (3) *Development and tubal transport of ova*, and (4) *Implantation*. In the present paper, an attempt has been made to review critically the current status of non-steroidal compounds interfering with these steps, and the prospects of their use as antifertility agents for the human female. The coverage of literature has been pertinent, but not inclusive, since several extensive reviews are already available on the subject[1-4].

Antiovulatory Agents

Ovulation blockage via inhibition of central nervous system (CNS)-pituitary mechanisms — Of the agents listed in Table 1, only atrophine, morphine, barbiturates, chlorpromazine, Dibenamine, SKF-501, reserpine, gold thioglucose and probably estrogens inhibit ovulation through their effect on the CNS; with the rest, this remains a suggestion based on mostly circumstantial evidence. The neural mechanism causing ovulation block has been clearly elucidated only in the case of pentobarbital, atrophine and morphine; all of them bring about an elevation of the arousal threshold for electrical stimulation of the midbrain reticular formation in rats[9]. The role of reticular formation in spontaneous ovulation in this species is now well recognized[9]. Dibenamine and SKF-501 act via neural pathways exclusively in rabbits, since they effectively block ovulation if administered only during an extremely short critical period after coitus[5]. This is supported by the finding that SKF-501 fails to inhibit ovulation induced by posterior basal tuberal stimulation[8].

Reserpine blocks spontaneous ovulation in rats, possibly by interrupting afferent input to the midbrain reticular formation[7]. This suggestion was based on indirect evidence from EEG studies. The compound failed to modify the threshold for arousal to stimulation of the midbrain reticular formation, whereas it markedly elevated arousal thresholds in either the pontine tegmentum or the vicinity of the cerebellar dentate nucleus[7]. Whether the same neural mechanism is also valid for the rhesus monkey, in which reserpine has been shown to block ovulation[6], remains to be examined. In this connection, reference may be made to the interesting observation that a single subcutaneous injection of 50 μg of this compound to four-day old female rats delayed vaginal opening and caused prolonged periods of diestrus during adulthood, with a lowering of pituitary luteinizing hormone (LH) content[27]. Apparently, such neonatal reserpine treatment leads to a long-lasting disturbance in ovulatory mechanism in rats. It would be worth while to explore any such neonatal sterilizing effect of other *Rauwolfia* alkaloids, notably the isomers of reserpine.

Gold thioglucose is unique in that it causes persistent vaginal cornification and presumably disturbs ovulation after a single injection in both mice[16] and rats[17], through the production of lesions in the hypothalamic regulatory centres. It would be interesting to examine the effect of this compound in a primate species such as the rhesus monkey.

From practical contraception standpoint, there is hardly any prospect that the various categories of pharmacologic agents (antiadrenergics, anticholinergics, barbiturates, anaesthetics and the like) would ever be useful. Non-specificity of their action makes them items of purely academic interest. However, Jöchle[1] is of the opinion that a case could be made for the development of a non-toxic morphine analogue that is not addictive.

The well-authenticated antiovulatory effect of non-steroidal estrogens, such as diethylstilbestrol[3,11-13] and tri-*p*-anisylchlorethylene (TACE)[14,15] is believed to be mediated via the CNS, but the precise mechanisms have not been delineated. According to

TABLE 1 — ANTIOVULATORY AGENTS ACTING VIA INHIBITION OF CNS-PITUITARY MECHANISMS

Agent	Species	Reference
Chlorpromazine	Rat, rabbit	3, 5
Chlorphenothiazine	Rat	3
Reserpine	Rat, rhesus monkey	3, 6, 7
Tetrahydropyrenil methyl reserpine (SU-7064)	Rat	3
Morphine	Rat, rabbit	5
Antiadrenergics (Dibenamine, SKF-501)	do	5, 8
Anticholinergics (atrophine, Banthine, Pthilon)	do	5, 9
Anaesthetic (ether)	Rat	3
Barbiturates (Dial, Ipral, Amytal, Nembutal, phenobarbitone, Prominal, pentobarbital)	do	1, 3
Brain nor-epinephrine depletors (α-methyldopa, syrosyngopine, tetrabenzene)	do	10
Non-steroidal estrogens (diethylstilbestrol, TACE)	Different animal species and human female	3, 11-15
Gold thioglucose	Rat, mouse	16, 17
Pentolamine	Rat, rabbit	5
Priscoline	do	5
Procaine	do	5
Neo-Antergen	do	5
Tetraethylammonium	do	5
Hydroquinone	Rat	18
2,6-Dimethylhydroquinone (*m*-xylohydroquinone)	do	18, 19
1-α-Methylallylthiocarbamoyl-2-methyl-thiocarbamoylhydrazine (ICI 33828, Methallibure)	Fowl, rat, mouse, dog, pig, rhesus monkey, human male and female	20
α-α-Dimethyl-10β-naphthyl-2-valeric acid	Rat	19
α-α-Dimethyl-5,6,7,8-tetrahydronaphthyl-2-valeric acid	do	19
Triphenylethylene derivatives	do	21, 22
Diphenylhydantoin	do	23
Tricyclopromine	do	24
Bis (*p*-acetoxyphenyl)-cyclohexilide methane (F6066)	Rat, mouse, rabbit, human male and female	25
Indole compounds	Rabbit	26

Flerko[28], natural estrogens inhibit the secretion of pituitary gonadotrophin by acting on the paraventricular nuclei of the hypothalamus. By analogy, such a mechanism may as well be operative with non-steroidal estrogens. However, the antiovulatory effect of diethylstilbestrol may be in part due to a direct action on the ovary. This, in fact, has been indicated in recent clinical investigations[12]. It has been observed that in normally cycling women selected on the basis of urinary total gonadotrophin excretion rate, basal body temperature (BBT), karyopyenotic index and 'spinbarkeit', the ovulation is delayed for 8-10 days after a single oral dose of 20 mg of diethylstilbestrol, as judged by all these parameters and the onset of withdrawal bleeding, absence of corpus luteum at laparotomy and endometrial biopsy picture. During the treated cycle two peaks of urinary gonadotrophin have been noted: the first coincides with the ovulation peak of the control cycle, and the second occurs 8-10 days later. When the same dose of the estrogen was given on day 7, 8, 9 or 10 of the cycle, menstruation occurred at the expected time. However, only one gonadotrophin peak was observed. The occurrence of the first gonadotrophin peak and the delayed ovulation are considered as indications of dissociability of the central and peripheral actions of diethylstilbestrol. This is interpreted in two ways: (1) the total urinary gonadotrophin peak is considered to reflect an altered FSH : LH ratio leading to disturbance in ovulation, and (2) ovulation is blocked directly at the level of the ovary. Apparently, differential assays of urinary and serum FSH and LH are expected to provide more meaningful information on this point.

The possibility of using diethylstilbestrol as an oral contraceptive has been examined in detail in a carefully designed clinical study[11]. Eighty-six highly fertile women of average age 28 years received 2 mg of the compound from day 1 to 20 of each cycle for 105 women years. During this period, only 3 pregnancies occurred, giving a net contraceptive efficacy rate of 94%. The side effects observed were nausea in 11 women, and breakthrough bleeding in 38, which was severe in 5 cases. Similarly, Martinez-Manautou *et al*[29] obtained more effective and consistent ovulation control with diethylstilbestrol than with natural estrogens in 128 fertile women for 247 cycles. They also believe that diethylstilbestrol acts partly via CNS mechanisms and partly by a direct action on the ovary[12].

TACE (tri-*p*-anisylchlorethylene), a depot forming synthetic estrogen, has been found to inhibit ovulation in rats[15] and women[14]. In the former species, fertility is reduced to nil.

It thus appears that synthetic non-steroidal estrogens are effective antifertility agents with no worse side effects than those usually encountered with steroidal estrogen-progestogen combinations[3]. Clinical studies with other non-steroidal estrogenic compounds (for which adequate background animal data are available) may lead to useful practical results in relation to control of ovulation.

Of the other agents listed in Table 1, Methallibure (ICI 33828), triphenylethylene derivatives and F6066 merit particular consideration.

The chemistry and biologic properties of Methallibure have been reviewed in detail by Walpole[20]. It is an effective inhibitor of pituitary gonadotrophin in a variety of animal species, including rhesus monkeys. In clinical studies, Methallibure has been found to reduce the urinary excretion of pituitary gonadotrophin in post-menopausal women, in women of reproductive age, and in male patients suffering from prostatic carcinoma with elevated urinary level of gonadotrophin; so much so that in a post-menopausal subject oral administration of the compound (10 mg/kg daily) caused a reduction in urinary gonadotrophin to a level far too low to be measured. At a different dose (300 mg

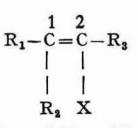
daily), the effect was, however, somewhat inconsistent[29].

In normal menstruating women, these relatively large doses of Methallibure given from early in the cycle have been shown to reduce the urinary excretion of gonadotrophin and estrogens to very low levels, and to prevent the post-ovulatory rise in pregnanediol excretion; ovulation was presumably inhibited and menstruation was suppressed in the treatment cycle[20]. On the other hand, when given from early in the menstrual cycle in a total daily dose of 50 mg ovulation was suppressed without a disturbance in pituitary gonadotrophic activity[29]. A direct action of the compound on the ovary, or a differential response of FSH and LH is indicated[20]. In an unconfirmed report, Mears[30] found that oral administration of 50 mg of Methallibure from fifth day of the cycle for 20 days to normal menstruating women inhibited ovulation without disturbing the menstrual cycle. In prostatic carcinoma cases, however, although the compound reduced the level of urinary gonadotrophin, the clinical response was not as good as with estrogens[20].

Some subjects in all the above-mentioned studies complained of side effects at all dose levels down to 50 mg. These included anorexia, nausea and occasionally vomiting, lethargy, and somnolence[20]. The latter suggest action of Methallibure at the CNS level. The glucocorticoid excretion is not altered, but the thyroid function is disturbed both in animals and in human subjects[20]. The nature of this disturbance is complex and has been considered in detail[20]. In brief, Methallibure interferes directly with the uptake and protein-binding of ^{131}I by the thyroid in addition to exerting a possible inhibitory effect on pituitary thyrotrophic activity.

Apart from the clinical investigations cited above, there has been no report of contraceptive trials of Methallibure in women. Apparently, the side effects of the compound precluded such trials. Nevertheless, the leads obtained have been valuable and may form the basis of synthesis of other compounds of this series free from side effects, but retaining potent antiovulatory activity.

Boris and his associates[21,22] synthesized a series of triphenylethylenes (I) and evaluated their antigonadotrophic activity by immature rat testis and prostatic weight method.



R_1, R_2 and R_3 = Phenyl
X = H or Br

I

The following structure-activity relationship appears to be valid:

(1) Loss of antigonadotrophin activity occurred when (i) R_2 was pyridine, dimethylixozole, cyclobutyl or cyclopentyl; (ii) R_1 and R_2 were bridged; (iii) a cyclopentyl group was substituted for ethylene group; and (iv) nitrogen was substituted for C_2.

(2) Enhancement of antigonadotrophin activity was obtained when X was bromine as compared to hydrogen.

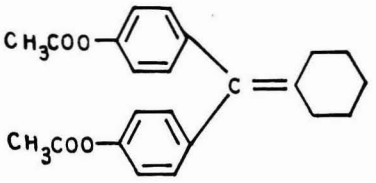
(3) *Cis* and *trans* isomers were almost equipotent with respect to antigonadotrophin activity.

(4) All active compounds were estrogenic; antigonadotrophin potency was related directly to estrogenicity. Thus, bromotriphenylethylene, which showed maximal antigonadotrophin activity, was also most potent with regard to estrogenicity. A separation between the two properties has not been observed.

(5) None of the compounds showed antiestrogenic activity.

Triphenylethylene derivatives, particularly the bromo compound, have not been tested specifically for antiovulatory and antifertility activities. The details of its other biologic profile are also not on record. Further investigations on this compound are indicated.

Bis (*p*-acetoxyphenyl)cyclohexylidene-methane (F6066) (II) has been shown to reduce fertility in rodent species, apparently through its antigonadotrophin activity[25]. It is effective by oral and parenteral routes and has weak estrogenic property in rats and mice. However, it has a more favourable ratio of pituitary inhibiting activity to estrogenicity than the conventional estrogens. The compound is devoid of anabolic, diuretic and anti-implantation effects; testis and prostatic weight in rats is reduced, and no effect on lactation is seen. In male rats spermatogenesis is arrested and Leydig cells are reduced in number; in females there is increased atresia of the follicles. The acute toxicity in mice is low (LD_{50}>1600 mg/kg); no signs of toxicity have been found in rats in a 15-week test for chronic toxicity, except a little inhibition of growth and some loss of appetite. Autoradiographic studies have shown that the compound is accumulated mainly in the corpora lutea and to a lesser extent in the pituitary, adrenal cortex, endometrium, interstitial tissue of the gonads, bile and liver. In rabbits and man F6066 is excreted mainly in faeces after oral or parenteral administration.



II

The observation that F6066 has relatively more potent antigonadotrophin than estrogenic activity in animals formed the basis of its clinical trial in human female and male. In the former the urinary gonadotrophin and estrogen excretion was reduced to unmeasurable quantities after oral administration of the compound. In male patients with prostatic cancer a favourable effect comparable to that exerted by diethylstilbestrol but without

feminization was noticed. Apparently, F6066 is a very promising compound and deserves extensive contraceptive trials in women. Synthesis and antifertility screening of analogues of F6066 may also lead to interesting results. From the favourable clinical response of prostatic carcinoma patients, it would appear worth while to undertake clinical trials of this compound as a male oral contraceptive.

Ovulation blockage via interference with gonadotrophin action at periphery — Agents blocking ovulation through interference with gonadotrophin action at the periphery are listed in Table 2. In most of the animal studies the general procedure has been to assess the inhibitory effect of the compound on an ovulatory (or superovulatory) regime of exogenous gonadotrophins (PMS, HCG or their combination; LH; pituitary extract). Hypophysectomized animals have also been used in more critical experiments to eliminate any central effect of gonadotrophins such as PMS[3].

Two extensive investigations deserve particular mention. Pincus[3] and his associates studied the effect of a large number of CNS depressants on PMS +HCG-induced ovulation in immature mice and found marked antiovulatory activity with Equanil, Chlorpromazine, Trilafon, Paxitol, Compazine, morphine and reserpine. Reserpine was most potent, since it reduced the number of ova ovulated from 25 in controls to 4 at a dose of 0·01 mg per mouse. A similar effect of the drug was seen in hypophysectomized immature rats subjected to superovulatory doses of PMS and HCG. Apparently, a direct effect on the follicles is indicated.

Kar *et al*[34] investigated the inhibitory effect of a large number of compounds on PMS-induced ovulation in immature rats. Positive antiovulatory effect was found with Vanillin, 2,3,5-trimethylhydroquinone, 4-methyl uracil and chloroacetocatechol. The latter proved to be the most active compound in the dose range 0·5-2·0 mg/rat. However, detailed antifertility trials of this compound in rats yielded negative results. It was also toxic.

Of the rest of the agents which have shown one or other degree of inhibitory effects on oxogenous gonadotrophin-induced ovulation, mention may be made of the antigonadotrophic factors isolated from pituitary, foetal serum, urine and the pineal gland[3].

Crude preparations of pituitary FSH and LH inhibit the potency of PMS and HCG in test animals, but with purification, particularly of FSH, this effect apparently disappears, indicating loss of the accompanying inhibitor substance. An antigonadotrophin substance has been found in human foetal serum, which blocks the action of HCG. A FSH inhibitor substance has been isolated from bovine serum, which is non-lipid, non-protein, water soluble, dialysable and thermolabile. A gonadotrophin inhibiting substance effective against HCG was first isolated from children's urine. Later, this substance was found in the urine of adult individuals of all ages. It is a heat-stable material, soluble in ether or 95% ethanol and inhibits pituitary LH action but not FSH. More recently, a FSH inhibitor has been isolated from the urine of rhesus monkeys, which may be a polypeptide.

The presumed pineal factor has been named 'anestrin', since it is antigonadotrophin only in female rats. Both melatonin (N-acetyl-5-methoxytryptamine) which occurs in pineal gland and its probable metabolite, 5-methoxytryptophal, are antigonadotrophin in rats. It has been suggested that pineal methoxyindoles are the active pineal material.

The action of the antibiotic, actinomycin-D, is interesting, since when injected directly into the preovulatory follicles of the rabbit it inhibits LH action[37]. It is believed that the antibiotic blocks the LH-stimulated synthesis of an enzyme by the granulosa cells, which is responsible for the rupture of the follicular wall.

From a critical consideration of these various antigonadotrophic substances, it seems doubtful whether any of them will find application as a contraceptive. This comment does not, however, apply to diethylstilbestrol, since, as pointed out earlier, it inhibits ovulation partly by peripheral mechanisms[11-13].

Ovicidal agents — Selenium dioxide added to drinking water exerts ovicidal effect in rats[1]. More interesting perhaps is the effect of cadmium salts. In prepuberal rats a single subcutaneous injection of cadmium chloride (10 mg/kg) causes total degeneration of the existing follicles, but the primordial oocytes are spared, which eventually develop into Graafian follicles[38]; the latter ovulate and are fertilized. The ovaries of adult rats are somehow resistant to the ovicidal action of the salt.

TABLE 2 — AGENTS INTERFERING WITH GONADOTROPHIN ACTION AT THE PERIPHERY

Agent	Species	Reference
Trimethylquinone	Rat	31
2-Hydroxy-3-(3-methyl-2 butenyl) naphthoquinone (Lapachol)	do	31
Polyphloretin phosphate (hyaluronidase inhibitor)	Rabbit	1
Lithospermic acid (oxidized polyphenolic acid from *Lithospermum ruderale*)	Fowl, rat	32
Thyroxine	Rat	33
Lysozyme	Rabbit	3
Chloroacetocatechol	Rat	34
Vanillin	do	34
2,3,5-Trimethylhydroquinone	do	34
4-Methyl uracil	do	34
CNS drugs (Trilafen, Paxitol, Compazine, reserpine)	Mouse, rat	3
5-Hydroxy tryptamine	Rat	35
Lysergic acid diethylamide (LSD), Methysergide	Mouse	36 1
Phenelzine	Rat	1
Diethylstilbestrol	Different animal species, human female	3, 11-15
Antigonadotrophic factors (from pituitary, foetal serum and urine; and pineal gland)	Human, cattle, rats	3
2-Amino-5-nitrothiazole	Fowl, rat	20
Actinomycin-D	Rabbit	37

However, a single intraovarian injection has been shown to destroy the entire oocyte and follicle population in guinea-pigs[39], goat[40] and cow[41]; the animals become permanently sterile. The effect is apparently specific, since the administration of zinc acetate in an equimolar dose has no untoward influence on ova[39]. It is worth noting that the antifollicular effect of cadmium chloride in prepuberal rats can be prevented by concurrent administration of zinc acetate or selenium dioxide[47].

A single intraperitoneal injection of Myleran (10 mg/kg) to pregnant rats 5-7 days before parturition causes complete sterility of female offsprings, apparently through a lethal action on oogonia during foetal life[42-44]. Administration of this drug to a pregnant woman evoked a similar sterilizing effect on the ovary of the offspring[43].

It has been claimed[45] that combined administration of chlorambucil and Prednisolone to women in their 50 and even under 40 causes destruction of the primordial oocytes. The same effect has been reported to be achieved in women by intra-aortic infusion of cyclophosphamide (Cytoxan)[45].

Forced inhalation of 2-chloro-1,3-butadiene (Chloroprene) by rats at the rate of 0·5 mg daily for 1-7 months markedly increased the rate of follicular atresia and disturbed estrus cycle[46]. This finding may be important in relation to the control of wild rat population. The compound is apparently toxic, since it causes degenerative changes in parenchymatous organs other than the ovary.

The ovicidal agents listed in Table 3 appear to be of academic interest only with hardly any prospect of application as contraceptives. However, they may be useful in the veterinary and animal husbandry field for livestock sterilization purpose. As an instance, a simple and bloodless method for permanent sterilization of scrub cows has been developed involving a single intraovarian injection of cadmium chloride[41]. This technique is expected to be helpful to countries like India burdened with a very large unproductive cattle population.

Agents interfering with estrus cycle and/or reducing fertility — The compounds listed in Table 4 have been reported to disturb estrus cycle and/or exert antifertility effect in animals through unknown mechanisms. Nikoceptin[57] and Galatoceptin[58], compounds of undisclosed chemical composition, and ascorbic acid[59] have been claimed to be effective oral contraceptives in women.

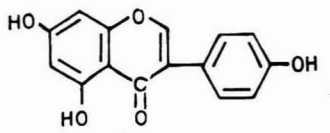
TABLE 3 — OVICIDAL AGENTS

Agent	Species	Reference
Selenium	Rat	1
Cadmium	Rat, guinea-pig, goat, cow	38-41
Alkylating agents (Myleran or Busulphan)	Rat, human female	42-44
Chlorambucil + Prednisolone	Human female	45
Cyclophosphamide (Cytoxan)	do	45
2-Chloro-1,3-butadiene (Chloroprene)	Rat	46

TABLE 4 — AGENTS INTERFERING WITH ESTRUS CYCLE AND/OR REDUCE FERTILITY

Agent	Species	Reference
Dimethylphosphate	Rat	3
Bromine	do	1
Aluminium salts	do	3
Benzpyrine	do	48
Anasanillic acid	do	49
Cyclopropenoid fatty acids	do	50
Genistein and related isoflavones	Domestic animals, rodents	51
Erucic acid	Rat	3
Butryophenone	do	52
Alkylene-diamine derivatives (insect chemosterilants)	Housefly	53
Retinoic acid	Rat	54
Chloroguanide (antimalarial)	do	3
Mimosine	do	55
Guanylhydrazones (antifolic acid ?)	do	3
Resorylic acid lactones (a type of fungus fermentation product)	do	56
Nikoceptin and Galatoceptin	Human female	57, 58
Ascorbic acid	do	59
Byakangelicin (alkaloid from *Ferula alliaceae* fruit)	Rat	60

Of the other compounds, the effect of genistein (III) and related isoflavones[51], alkylene-diamines[53] and mimosine[55] may be highlighted. Genistein was isolated from subterranean clover (*Trifolium subterraneum*) and found to be estrogenic in mice, which apparently accounted for infertility in sheep grazing on pastures of this plant. Further investigation of the saponified extracts of the plant yielded other estrogenically active products like 4-methyl ether of genistein (biochenin-A), and a fraction with still greater estrogenic potency, which has not yet been isolated in pure form.



III

Synthetic analogues of isoflavones, isoflavonones, isoflavenes and other plant products (steroids, stilbenes) with estrogenic activity have been reviewed extensively[61]. Some of them may be investigated for antifertility activity.

Alkylating agents derived from α-ω-alkylene-diamines were synthesized[53] and tested in houseflies for chemosterilant activity, which varied with the distance between two alkylating groups. Most potent compounds were N,N′-bis(azirideneacetyl)-1,8-octamethylenediamine and N,N′-bis(azirideneacetyl)-1,9-menoethylene diamine. In view of the

potent antispermatogenic effect of bis(dichloroacetyl)-diamines in animals and men[3], these related chemosterilants merit antifertility trials in male and female animals.

Mimosine is a toxic amino acid occurring in various leguminous plants[55]. Feeding of this substance (0·5% in an experimental diet) to female rats made them reversibly sterile. Mimosime has some structural similarities with pyridoxine group of vitamins, and vitamin B_6 antagonism may be responsible for its antifertility effect.

Agents Interfering with Tubal Events

Fertilization — Based on the well-established occurrence of hyaluronidase, and the now untenable notion that a 'sperm swarm' was necessary to produce an amount of this enzyme sufficient to denude ova[3], it was considered possible that hyaluronidase inhibitors might act as antifertility agents. In point of fact, several synthetic analogues of hyaluronic acid[62] and trigentistic acid[63] were found to inhibit fertilization in rabbits when mixed with sperm suspensions or instilled intravaginally preceding coitus, but not on parenteral administration. Apparently, these and other large molecular weight antihyaluronidases (naturally occurring serum factor, certain synthetic polymers)[3] were unable to penetrate to the site of fertilization when administered parenterally. The claim for oral antifertility action of the hyaluronidase inhibitor, phosphorylated hesperidine, could not be confirmed[3]. However, the antifertility effect of another inhibitor of this enzyme (ammonium aurine tricarboxylate) in male rats is interesting and requires further study, since sperm morphology and motility are not altered[3]. It is possible that either sperm penetration of the cervical mucus or of the ovum was prevented.

Pincus[3] is of the opinion that research on antifertilization agents has been abandoned rather unwisely, and a revival of interest is highly desirable. The advances in our knowledge of the chemistry of the 'tubal factor' for ova denudation, which has recently been identified in the Fallopian tube fluid[64], may lead to the development of parenterally effective antifertilization agents. In this connection, due consideration should also be given to possible chemical interference with sperm capacitation process.

Ova development — A direct antimitotic effect of colchicine on rabbit ova *in vitro* has long been known[3]. The derivatives of colchicine, Colcemid and Thiocolceran, have been shown to be lethal to the clearing of ova and the blastocysts, causing degeneration of the embryonic disc through mitotic arrest when injected into pregnant rabbits[65]. They are transported to ova via the uterine fluid. Several investigators reported marked direct toxic action of Colcemid on the foetus of rats and rabbits when injected during pregnancy[66]. The compound exerts its maximum effect on days 12-15 of pregnancy; a single subcutaneous injection (0·5 mg/kg) causes complete destruction of the litter. Earlier and later in pregnancy larger doses are required, which are toxic to mother. However, her reproductive potential is not impaired. The compound is not effective orally. It is interesting that after injection into pregnant rhesus monkey (2 mg/kg) and women normal foetuses were born[66]. Apparently, there is a species difference in the action of this compound on the foetus and perhaps also on the blastocyst.

Other antimitotic agents included in Table 5 have been reported to cause degeneration of cleaving ova and mitotic arrest in the blastocyst of rats and/or rabbits, and destruction (or teratogenicity) of foetuses when injected during pregnancy[3,65]. A species difference is, again, indicated, since one of the compounds (BW57-323H) when injected (7·5 mg/kg, 3 injections daily) into a pregnant rhesus monkey on days 28, 29 and 30 exerted no adverse effect on the foetus[66].

Culture of rabbit ova *in vitro* with penicillin, penicillin-G, chloromycetin and paromomycin at

TABLE 5 — AGENTS INTERFERING WITH OVA DEVELOPMENT

Agent	Species	Reference
Cytotoxic agents		
Colchicine and derivatives, N-desacetyl-N-methylcolchicine (Colcemid), N-desacetyl-thiocolchicine (Thiocolceran)	Rabbit, rhesus monkey, human female	3, 65, 66
2-Amino-6-(1′-methyl-4′-nitro-5′-imidazolyl)-mercaptopurine (BW57-323H), 6-mercaptopurine, 8-azaguanidine, triethylene thiophosphoramide (Thio-TEPA), β-bis-1,6-chloroethyl-amino-D-mannitol (Degranol), triethylene-melamine (TEM), BAL derivatives, ethylene-imino derivatives aminopterin, azaserine, diazooxonorleucine, diazoacetylserine	Rabbit, rat, rhesus monkey	1, 3, 65, 66
d-Usinic acid	Rat	3
Podophyllotoxin	do	3
Vinca leucoblastine from *Vinca rosea*	Rat, rabbit	66, 67
Antibiotics (penicillin, chloromycetin, paromomycin, penicillin-G)	Rabbit	3
2-Deoxy-*d*-glucose	do	68
Staphylococcal alpha toxin	do	69
1-(*p*-2-Diethylamino-ethoxyphenyl)-1-phenyl-2-P-anisylethanol (MER-25)	Rat, rabbit	70, 71
1-(*p*-2-Diethylamino-ethoxyphenyl)-1,2-diphenyl-2-chloroethylene (Clomiphene; MRL-41)	do	71-73
2-[*p*-{6-Methoxy-2-(*p*-methoxyphenyl)-inden-3 yl}-phenoxy]-triethylamine hydrochloride (U-11555A)	do	71, 74, 75
Diethylstilbestrol and derivatives	Rodents	3
Methallibure	Rat	76

relatively high concentrations prevents their development on transfer to recipients[3]. No *in vivo* effect of these antibiotics on ova has been reported.

2-Deoxy-*d*-glucose (2-DG), an analogue of glucose, causes serious and selective damage to the embryonic disc of rabbit blastocysts when administered on days 5-6 of pregnancy[68]. The compound was ineffective up to day 4 of pregnancy and is believed to interfere with carbohydrate metabolism of the embryonal disc cells by its ATP-depleting property.

Staphylococcal alpha toxins have been reported to damage cleaving ova of rabbits[69]. The effect is maximal during the later stages of cleavage due to increased permeability of the egg membrane to the toxin. Mass foetal death is noticed around day 15 of pregnancy.

Triphenylethylene derivatives (MER-25 and Clomiphene) have been shown to be toxic to the cleaving ova and blastocysts in rats and rabbits when administered on days 1-3 of pregnancy[70-73]. In delayed implantation test in rats this effect of Clomiphene has also been observed[77]. It is interesting that the antizygotic effect of MER-25 may be mediated via a reduction in tubal secretion[78]. However, a direct effect on cleaving ova *in vitro* has also been demonstrated[3].

A 2,3-diphenylindene derivative, U-11555A, is believed to have blastotoxic effect in rats and rabbits[71,74]. However, delayed implantation test and blastocyst transfer studies in rats have excluded this possibility. This compound has no effect on volume of the Fallopian tube fluid in rabbits[79]. Further details about this and other triphenylethylene derivatives will be considered in the subsequent sections.

Pincus[3] is of the opinion that the estrogens may also exert a direct toxic effect on ova of rodents if administered in high doses during late cleavage. In point of fact, such an effect on rabbit ova has been reported after diethylstilbestrol administration[75].

Methallibure administered orally to rats on days 2-4 of pregnancy prevented implantation; about 66% of ova failed to implant[76]. There was heavy foetal loss and the development of the surviving ones was considerably retarded. The compound also showed antideciduomagenic property in pseudopregnant animals. It was suggested that intrinsic pituitary-inhibiting property of the compound[20] disturbed the hormonal balance necessary for the maintenance of pregnancy. However, the high percentage of preimplantation ova loss may also be due to a direct blastotoxic action of the compound.

Ova transport — It is now well documented that oral administration or injection of steroidal and non-steroidal estrogens after coitus interferes with tubal transport of ova in several rodent species[3]. Depending upon the dose and species, the transport of ova is either speeded up or retarded. In either case, implantation does not occur due to the resultant ovoendometrial asynchrony. The precise mechanism by which estrogens cause such interference with ova transport is, however, imperfectly understood. Alterations in tubal motility, ciliary movement, fluid volume and some metabolic

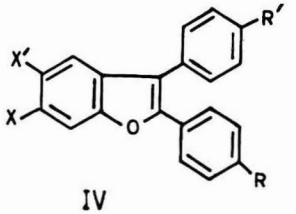
TABLE 6 — AGENTS INTERFERING WITH TUBAL TRANSPORT OF OVA

Agent	Species	Reference
Diethylstilbestrol and non-steroidal estrogens	Rodents	3
Clomiphene, MER-25	Rat, rabbit	3
U-11555A	Rat	80
[1-{2-(*p*-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthyl)phenoxy} ethyl]-pyrrolidine hydrochloride (U-11100A)	do	81
2,3-Diphenylbenzofurans 2-Phenyl-3-*p*-β-pyrrolidinoethoxyphenyl-6-methoxy-benzofuran hydrochloride (DBF)	Rat, mouse, rabbit, rhesus monkey	83, 84
Triphenylethylene derivatives (ICI 46474 and ICI 41699)	Rat	85-87
Reserpine	Mouse	88

incompatibility between ova and the tubal milieu may be involved. The subject has been reviewed extensively by Pincus[3].

Clomiphene, MER-25, U-11555A and a diphenyldihydronaphthalene derivative (U-11100A) have been reported to cause rapid expulsion of ova through the Fallopian tubes[3,80,81] (Table 6). It seems that inherent estrogenicity of these compounds is involved in this effect. In a recent histochemical study it has been shown that U-11555A causes a reduction in PAS positive material, sudanophilic lipids, mucopolysaccharides and alkaline phosphatase in the uterine and tubal epithelium of rats[82].

Grover *et al*[83] reported the synthesis and evaluation of post-coital antifertility activity of 2,3-diphenylbenzofurans (IV). The most potent compound of this series (2-phenyl-3-*p*-β-pyrrolidinoethoxyphenyl-6-methoxy-benzofuran hydrochloride, DBF) caused 100% reduction of fertility in rats and mice when administered orally on days 1-5, or once on day 1, 2 or 3 post-coitum[84]. The minimal effective dose (med) on 5-day regime basis was 4 mg/kg, and on the single ingestion schedule was 20 mg/kg. In rabbit, the compound caused 93% reduction in fertility. The antifertility effect was, however, reversible in all species.



IV

DBF showed mild uterotrophic activity (28-31% of that of estrone) in rats when administered orally, but not after subcutaneous injection; it did not cause vaginal cornification. In immature rhesus

TABLE 7 — STRUCTURE-ACTIVITY RELATIONSHIP FOR 2,3-DIPHENYLBENZOFURANS (IV)

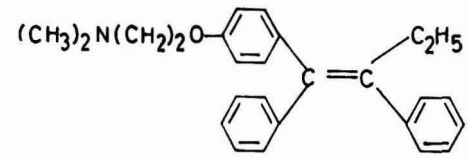
Compound No.	X	X′	R	R′	Min 100% antifertility dose mg/kg, days 1-5 of pregnancy
1	OCH_3	H	H	$OCH_2CH_2N(C_2H_5)$	8
2	OCH_3	H	H	OCH_2CH_2N 	4 (single day 20)
3	OCH_3	OCH_3	H	$OCH_2CH_2N(C_2H_5)_2$	80
4	CH_3	CH_3	H	$OCH_2CH_2N(C_2H_5)_2$	>30
5	CH_2CH_2N 	H	OCH_3	OCH_3	>20
6	CH_3	CH_3	$OCH_2CH_2N(C_2H_5)_2$	$OCH_2CH_2N(C_2H_5)_2$	>20

monkeys, the compound (20 mg/kg daily/5 days, oral) did not exert any estrogenic affect on uterine weight, endometrial histology, vaginal smear picture, sex skin or breasts. The duration of uterotrophic activity in rats was considerably less than that of estrone. It was devoid of antiestrogenic, progestational, androgenic or antiandrogenic properties, but interfered with the action of progesterone in 'delayed implantation' test in rats. There was no effect on pituitary, adrenal and thyroid function; in rhesus monkeys, the menstrual cycle was not disturbed. The compound caused foetal resorption (about 45%), but no teratogenicity or genital abnormalities of the offspring; the post-natal sexual development and subsequent fertility (studied for 2 generations) remained unimpaired. The antifertility effect was due to premature expulsion of ova from the tubes; the fertilization process was unaffected.

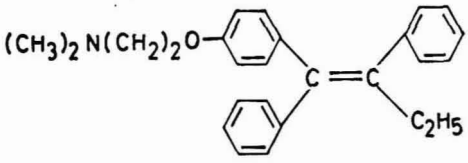
The LD_{50} in rats (intraperitoneal) was 388 mg/kg and the maximal tolerable dose in mice by the same route was 300 mg/kg. No noteworthy gross pharmacological effects were observed. However, in chronic toxicity studies in rats DBF showed a high incidence of pulmonary inflammation.

Structure-activity relationship studies (Table 7) showed that the presence of a methoxy group at position 6 increased the antifertility activity as compared to the basic benzofuran molecule or the 6-methyl/pyrrolidino-substituted molecule. Another methoxy group at position 5 had no additive effect on potency. The replacement of diethylamino with pyrrolidino group increased the antifertility activity by a factor of 2.

Harper and Walpole[85-87] investigated the antifertility activity of a triphenylethylene derivative, 1-(*p*-β-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene. The *cis* isomer (ICI 41699; V) was a potent estrogen in rat and mouse tests, antigonadotrophic and prevented implantation when given on days 1-4 of pregnancy at doses needed to induce vaginal cornification. It had no antiestrogenic activity. The *trans* isomer (ICI 46474; VI) was weakly and atypically estrogenic, antiestrogenic and mildly antigonadotrophic. Since it was more potent than the *cis* isomer in preventing implantation, detailed studies were conducted with it.



V



VI

The compound ICI 46474 prevented pregnancy in rats when administered orally (30 μg/kg) on days 2-4 post-coitum. A single oral dose (120 μg/kg) on day 4 of pregnancy was found to be most effective. Even 0·25 mg/kg twice a week was sufficient to prevent pregnancy for 12 weeks. In mice, the effective dose was 120 μg/kg (days 2-7 post-coitum).

The *modus operandi* of the compound is interesting. A single oral dose on day 1 or 2 post-coitum prevented implantation in rats by accelerating tubal transport of ova. Since this was partially blocked by progesterone, it was suggested that this effect was due to estrogenicity of the compound. On the other hand, when given on day 4 it prevented pregnancy by blocking 'estrogen surge', which is believed to occur on that day and held to be crucial for implantation in this species. This is apparently due to the inherent antiestrogenic activity of the compound, since blastocysts could be made to implant by giving a single injection of estrogen.

LD_{50} of ICI 46474 in mice was 3100 mg/kg oral and 270 mg/kg intraperitoneal. It caused a marked decrease in serum cholesterol of rats when fed at

0·01% level in diet without affecting the cholesterol content of the liver. The desmosterol content of the liver and serum was not affected either. Particular attention was paid to the effect of ICI 46474 on cholersterol metabolism, because MER-29, a member of a related series of compounds, was shown to cause loss of hair, cutaneous ichthyosis and cataract in patients through blockage of cholesterol biosynthesis, and the consequent hypocholesteremia. Sterol precursors of cholesterol (desmosterol, lanosterol) have been shown to accumulate in the affected tissues (skin, liver, serum) of rats leading to these toxic effects.

The compound ICI 46474 appears to be a promising anti-implantation agent. Further details about this compound and the results of any human trial will be awaited with interest.

Post-coital administration of reserpine caused a dose-dependent decrease in the rate of ova transport through the Fallopian tube of mice[88]. A complete 'tube-lock' condition was produced by a 10 mg/kg dose; ova development was also arrested. These effects were not due to an impairment of ciliary movement nor decrease in volume of the tubal fluid.

Anti-implantation Agents

Pharmacologic agents, such as Pilocarpine and Physostignin (parasympathomimetics), and sympatholytics listed in Table 8 have been reported to inhibit implantation in rats when administered post-coitum[1,89]. The most effective among the sympatholytics were piperoxan derivatives which caused 70-90% prevention of implantation when given on day 4 of pregnancy at the rate of 100-250 mg/kg. It is possible that these agents interfered with implantation by stimulating unphysiologic motility of the uterus[1].

Shelesnyak[90] investigated the anti-implantation effect of several ergot alkaloids (ergocornine, ergocryptine, ergosine) in rats. These compounds are believed to cause a decrease in progesterone level in the progravid animals through interference with luteal function at the pituitary level[101], leading to inhibition of decidualization. Of these alkaloids, ergocornine has been investigated extensively and besides rats, it has been found to be effective in mice[102]. A single subcutaneous injection (0·25-0·5 mg) on day 4 of pregnancy has been found to terminate pregnancy in mice. However, it is ineffective and toxic in rabbits; at higher doses (4-6 mg/kg) it causes death[66].

In limited clinical trials, post-coital administration of ergocornine has been found to terminate pregnancy[103]. Urinary pregnanediol output was depressed, suggesting a blockage of progesterone biosynthesis, possibly through inhibition of 3β-hydroxysteroid dehydrogenase activity[90]. These effects have not been confirmed[90a]; it is also ineffective in guinea-pigs[90b]. Further, for a consideration of the general use of this compound as an antifertility agent in women its inherent toxicity has to be kept in view[66].

Butazolidine has been reported to terminate pseudopregnancy in rats, possibly via a direct action on the CNS[2].

TABLE 8 — ANTI-IMPLANTATION AGENTS

Agent	Species	Reference
Parasympathomimetics (Pilocarpine, Physostignin)	Rat	1
Sympatholytics — Ergot alkaloids (Neo-gynergen), β-tetrahydronaphthylamines, 2-aminomethyl benzodioxanes, piperoxans	do	1, 89
Ergocornine, ergocryptine, ergosine (ergot alkaloids); butazolidine (3,5-dioxo-1,2-diphenyl-4-*n*-butylpyrazolidin)	Rat, human female	2, 90
Tranquillizers (reserpine, phenothiazine derivatives)	Rat	91
5-Hydroxy tryptamine	do	92
Monoamineoxidase inhibitors (hydrazine derivatives, iproniazid)	Mouse, rat, rabbit	92-94
Pyrathiazine, diphenylhydramine (antihistaminics), oxytocin, epinephrine, phenylbutazone (anti-inflammatory agent)	Rat	1, 90
Furazolidine	do	95
Phenolic valeronitriles	do	96
2,6-Dimethylhydroquinone (*m*-xylohydroquinone)	Rat, human female	97, 98
2,8-Dichloro-6,12-diphenyldibenzo(b,f)-(1,5)diazocine (U-10293)	Rat	99
Emetine dimer	do	100
Cadmium salts, cytotoxic agents, ethanol	do	103

The administration of reserpine (100 μg/100 g) on days 1-6 of pregnancy prevents implantation in rats. The blastocysts remain apparently normal and can be recovered from the uterine lumen on day 10 of pregnancy. Phenothiazine derivatives (chlorpromazine, thioproperzine, prochlorpemazine, perphenazine, chlorodeserpidine) similarly injected during the first 7 days or so of pregnancy (1-5 mg/100 g) have been reported to inhibit implantation in the same species[91]. Further, reserpine can prolong pregnancy by causing delayed implantation. It is believed that the tranquillizers disturb the implantation process by causing estrogen deficiency through a primary inhibitory action on hypothalamico-pituitary mechanisms.

Paulsen *et al*[92] observed that injection of 5-hydroxy tryptamine at the rate of 0·5 mg twice daily on days 1-6 post-coitum prevented pregnancy in mice, rats and rabbits. The same effect was observed in these species after subcutaneous injection of iproniazid (a monoamine oxidase inhibitor) at a dose of 5-10 mg on days 1-6 of pregnancy[94]. In addition, 5-hydroxy tryptamine terminated established pregnancy through a direct toxic action on the decidual tissue and partly by disturbing luteal function[12].

The antifertility activity of several hydrazine derivatives, all monoamine oxidase inhibitors, has been investigated in rats and mice. Compound

1275 [N-(1-methyl-2-phenoxyethyl)hydrazinium (1+) hydrogen maleate] has been found to interrupt pregnancy in mice at a dose of 0·5 mg/kg given on days 1-7 post-coitum[9]. The compound has been found to disturb estrus and implantation, which are believed to be related to its anti-inflammatory property, although an endocrine-mediated effect is not discounted.

Poulsen and Robson[104] observed that the administration of other hydrazine derivatives, such as β-phenylethyl hydrazine-hydrogen sulphate (phenelzine), *o*-chloro-β-phenylethyl hydrazine-dihydrogen sulphate, β-2,4-dimethylphenyl-ethyl hydrazine-dihydrogen sulphate, and *o*-methylphenyl-ethyl hydrazine (WL 31), on days 1-6 post-coitum inhibited pregnancy in mice. They also effectively interrupted established gestation in this species. These compounds act by reducing uterine sensitivity to progesterone and not by virtue of their monoamine oxidase inhibiting activity.

Shelesnyak[90] postulated that a sequence of pre-implantation events begins with pituitary activation of predominantly progravid (rat) ovary to secrete a 'surge' of estrogen; this is followed by release of histamine, which transforms the endometrium into decidua, and subsequently a stage of progesterone support for development and maintenance of decidua for reception and nurture of the blastocyst. He has marshalled imposing evidence in support of his hypothesis[90,105].

Estrogen is known to increase the concentration of histamine in the rat uterus[106]. Administration of MER-25, an active antiestrogen, on the day of estrogen 'surge', inhibits implantation in rats, and prevents the formation of decidua that is generally seen after a single intraperitoneal dose of the histamine-releaser, pyrathiazine hydrochloride[90]. Similarly, a single injection of estrogen to rats ovariectomized immediately before the 'surge' tended to restore the decidualization capacity of the endometrium[3]. Antihistaminics and agents markedly depleting histamine level have been reported to interfere with implantation and decidual reaction in this species most effectively when administered directly into the uterine lumen[90]. Curiously, oxytocin, epinephrine and certain other compounds such as phenylbutazone (anti-inflammatory agent), have also been found to block decidualization[1,90].

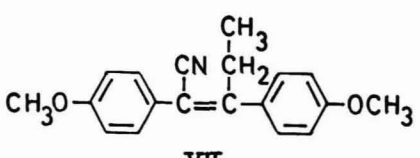
Nevertheless, Shelesnyak's attractive hypothesis, particularly the putative crucial role of histamine in implantation and decidualization, has not received general support. Many investigators could not confirm the deciduomagenic effect of histamine or histamine-releasers[3,107-109]. Emmens[110], suspecting the presence of possible estrogenic contaminants in histamine samples, suggests that histamine-induced deciduoma may be a low-dose estrogen phenomenon and that intrauterine antihistaminics may be merely toxic to the uterine tissue and not functionally suppressive. Of such dissident findings more recently reported, mention may be made of the one by Harper[111] who observed that pyrathiazine hydrochloride (pyrrolazoline), diphenylhydramine hydrochloride (Benadryl), isothiopendyl hydrochloride (Nilergex), promethiazine hydrochloride (Phenergen), phenindamine hydrazine tartrate (Theophorin) and methdilazine hydrochloride (Tacaryl) failed to prevent implantation in rats (except Tacaryl at very high doses) after parenteral administration. However, Shelesnyak[90] argues that the inability of the systematically administered antihistaminics to suppress decidualization and implantation may be due to their rapid detoxification and poor intrauterine concentration.

Banik and Ketchell[112] found that trauma was deciduomagenic to one uterine horn of pregnant and pseudopregnant rats, but histamine even in massive doses was ineffective in this respect for the contralateral horn. They concluded that histamine release is an effect and not a cause of deciduomagenic activity. This conclusion appears to be in keeping with the notion that a condition resembling tissue injury is simulated in the endometrium at the time of implantation[90]. In point of fact, suggestive evidence has been adduced by Psychoyos[113] who demonstrated increased capillary permeability and edema of the rat uterus at this time.

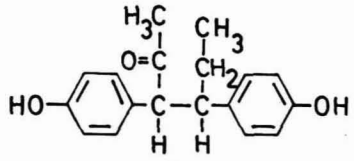
In a recent critical study, Cecil *et al*[114] have affirmed the non-specific nature of the role of histamine in implantation. They observed that intraluminal administration of histamine damages the rat uterus, and the increases in vascular permeability and water content are consequences of that injury. Tissue damage, irrespective of the cause, is known to evoke a diphasic pattern of response: an increase in vascular permeability (as determined by Pontamine sky blue procedure) within 30 min-1 hr, followed by a secondary peak of this reaction after 3-4 hr. Histamine and antihistaminic compounds evoked such typical diphasic response when instilled into the uterine lumen *pari passu* with indications of severe tissue injury (haemorrhage, clotting and epithelial denudation). It is interesting that administration of estradiol in 1·3% saline into the uterine lumen produced mild injury and the same pattern of diphasic response. However, subcutaneous injection of estrogen caused a peak only at 4 hr. Cecil *et al*[114] concluded that the intraluminal administration of any substance (including physiological agents such as estrogen) will cause tissue injury and diphasic changes in vascular permeability of the uterus. It is pertinent to add that the reports of anti-implantation activity of Phenylbutazone[1] and cortisone[115] have not been confirmed[90].

It thus appears that there is as yet no firm and unequivocal experimental basis for the role of histamine in implantation. Recently, doubt has been cast on the postulated mechanism of implantation[90] by Shelesnyak himself[116]; he found that MER-25 did not block histamine release that follows estrogen 'surge', but effectively prevented implantation. Moreover, there is no evidence to indicate that this mechanism of implantation proposed on the basis of studies conduced mainly with rats, is valid for the human female or infra-human primate species.

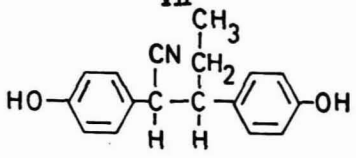
A single injection of furazolidine (1·0 mg/kg) on day 1 of pregnancy caused 90% prevention of pregnancy in mice[95]. The compound showed maximum effect (100%) when given on day 7 post-coitum.



VII



VIII



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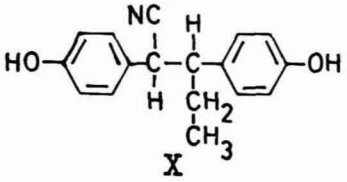


X

Phenolic valeronitriles (VII-X), when administered post-coitally, prevented implantation in rats[96]. These compounds are estrogenic, although their anti-implantation potency is 10-15 times greater than their estrogenic activity. Replacement of nitrile by acetyl group increased their estrogenicity, but decreased the antifertility potency.

2,6-Dimethylhydroquinone (*m*-xylohydroquinone), originally isolated from the oil of the field pea (*Pisium sativum*) and subsequently synthesized, evoked much interest because of the persistent claim that it is a potent oral contraceptive[98]. Ingestion of the compound (300-350 mg) on days 16 and 21 of the menstrual cycle has been reported to cause 50% reduction in fertility. On the basis of experiments with rats, the antifertility effect has been ascribed to an interference with the peripheral action of progesterone. This claim has not been confirmed[97]. The compound is, however, non-toxic.

Duncan *et al*[99] investigated the effect of a diazocine compound [2,8-dichloro-6,12-diphenyldibenzo(b,f)(1,5)diazocine, U-10293] on the fertility of female rats. Pregnancy was completely inhibited at a dose of 0·5 mg when given orally or subcutaneously for 7 days from the time of mating. A single dose before implantation was equally effective. The compound was estrogenic, antigonadotrophic, non-toxic and non-teratogenic. All these attributes seem to be favourable for undertaking a clinical trial of this compound.

A dimer of the potent amoebicidal drug emetine administered orally (0·3 mg/kg) 7 days before and 7 days after mating caused more than 90% prevention of pregnancy in rats, possibly through an interference with implantation[100]. However, the compound was toxic.

A single intrauterine instillation of cadmium sulphate ($0{\cdot}5\times10^{-2}M$), iodoacetate ($10^{-2}M$), podophyllin (in vaselin ointment, 5 mg/ml), colchicine (in saline, 0·5 mg/ml), Thio-Tepa (2 mg/ml) and ethanol (50 and 100%) prevented implantation in rats[103]. Hypertonic saline was ineffective. Cadmium, iodoacetate and ethanol produced a bilateral effect lasting for 1-2 months or longer, without inhibiting ovulation. Thio-Tepa exerted a unilateral influence for 2 months.

Emmens and coworkers[117-121] investigated a large number of analogues of diethylstilbestrol in rats, mice and rabbits for anti-implantation activity (Table 9). Some of these compounds are anti-estrogenic and proestrogenic, that is, they are metabolized to estrogens *in vivo*. Of these, the most potent compound was dimethylstilbestrol (DMS), which caused 50% failure of implantation in rabbits when injected on days 5-7 post-coitum at a dose of 25 mg. In rats and mice (med about

TABLE 9 — ANTI-IMPLANTATION AGENTS

Agent	Species	Reference
Non-steroidal estrogens: Diethylstilbestrol, dimethylstilbestrol, bibenzyl derivatives, Phloretin, parahydroxypropiophenone, [3-(6-methoxy-2-naphthyl)2,2-dimethylpentanoic acid, Vallestril]	Rodents, rhesus monkey, human female	2, 3, 79, 117-123
Clomiphene, MRL-37	Rhesus monkey, rat	73, 79, 121
2,3-Diphenylindenes	Rodents	79, 124, 125
1,2-Diphenyl-3,4-dihydronaphthalenes	Rodents, rhesus monkey	79, 126-128
1,2.3,4-Tetrahydro-1,2-diarylnaphthalenes	Rat	129, 130
5-(Phenoxymethyl)-2-oxazolidenethiones	do	131-134
3,4-Diphenylcoumarins	do	135, 136
3,4-Diphenylchromanes	do	147, 148
2-Methyl-3-ethyl-4-phenyl-Δ^4-cyclohexanecarboxylic acid (ORF-3858)	Rodents, rhesus monkey	79
[1-{2-(*p*-(α-(*p*-methoxyphenyl)-β-nitrostyryl)-phenoxy}ethyl]pyrrolidine (CN-55945-27)	Rat	137, 138
Isoflavone derivatives	do	139, 140
2,3-Diphenylindoles	do	141-143
2,3-Diphenylacrylophenones	do	144
Aromatic sulphur derivatives	do	145
66/179	Rodents, rhesus monkey	Kar, A. B., Kamboj, V. P., Setty, B. S. & Chandra, H., unpublished data
Triphenylnitroethylenes	Rat	146

50 μg, diethylstilbestrol, med about 0·1 μg) the compound prevented implantation effectively when injected on day 4 of pregnancy. In exhaustive studies on DMS and its congeners in mice, a remarkable parallelism was found to exist between their post-coital antifertility, antiestrogenic and proestrogenic potencies[118]. Of the other compounds in the stilbene series, dihydroxyalkanes were noted to be weak antiestrogens and failed to prevent implantation in fairly high doses. Emmens[120] is of the opinion that DMS and related compounds exert their anti-implantation effect by virtue of their estrogenicity rather than by their antiestrogenic property. This view is supported by the finding that DMS and estradiol are additive in inhibiting implantation and deciduoma formation in mice[119].

Morris and van Wagenen[123] investigated the post-coital antifertility efficacy of diethylstilbestrol in rhesus monkeys and women. In 28 rhesus monkeys, the compound was given for 6 days (1-25 mg) following positive mating over a period of 2 years; there was no pregnancy in spite of 321 positive matings. In 3 years of normal breeding prior to treatment there were 204 positive matings, resulting in 42 pregnancies. Similar results were obtained with estradiol (10 mg). There was no effect on the menstrual cycle, but sex skin became brighter and libido tended to increase. Oral or intramuscular injection of estrogens after implantation (on days 18-167) had no effect on the development and normalcy of the foetus.

Morris and van Wagenen[123] extended these studies on women who were either rape cases or volunteers. The rape cases received 50 mg of diethylstilbestrol for 4-6 days after exposure, which occurred mostly near the mid-cycle, and detected by ferning of cervical mucus and presence of sperms. In this small series no pregnancies occurred and the subsequent menstrual cycle continued undisturbed. Side effects, such as nausea and breast soreness, were of the usual estrogen type, which disappeared upon discontinuation of medication.

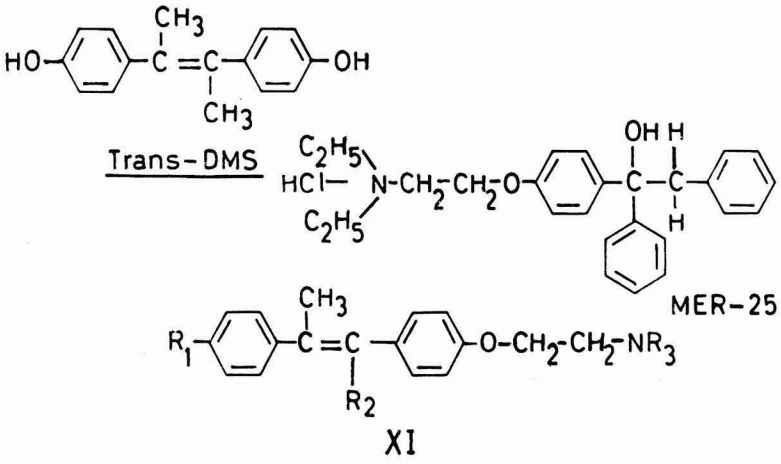
The limited number of volunteers provided an opportunity for more elaborate observations. In all cases sexual intercourse took place at mid-cycle near the time of the temperature rise. Fern crystallization and Huhner tests were positive in most subjects. The apparent effect of 5-50 mg of diethylstilbestrol or 0·5 mg of ethinyl estradiol was to counteract the thermogenic effect of progesterone on the biphasic temperature curve, or to shorten the luteal phase. Some noteworthy changes were observed in the endometrium: instead of a proliferative or hyperplastic condition, endometrial biopsies taken on post-ovulation days 5-7 and 10-12 showed a progestational effect with secretion in some instances on both sides of the nucleus, occasionally almost suggestive of an Arias-Stella reaction. The stroma was dense in some areas and markedly edematous in others. Basal vacuolation often persisted up to menstruation, sometimes giving an impression of early secretory phase picture late in cycle. No pregnancies, however, occurred in these cases.

The mechanism by which estrogens exerted such post-coital antifertility effect in women is unknown. Morris and van Wagenen[123] suggest that implantation is prevented through a hypothermic effect, which is a documented attribute of estrogens. However, from the nature of endometrial changes it would appear that an interference with post-ovulatory maturation of the endometrium, and ovo-endometrial asynchrony caused by a disturbance in tubal transport of ova may be critical factors involved in the failure of implantation.

Recently, Emmens[122] investigated the post-coital antifertility activity of bibenzyl (hexestrol-like) series, and compounds in which certain molecular configuration features of DMS and MER-25 were linked (XI). About 40 such compounds have been tested in mice with an upper dose limit of 1 mg. The structure-activity relationship of 6 of these compounds is shown in Table 10.

From the apparent coincidence of estrogenic and antifertility activity as indicated above, it was concluded that these compounds prevented implantation primarily by virtue of their estrogenicity.

Further detailed studies were conducted with simpler bibenzyl compounds (XII). Chemically,



XI

TABLE 10 — STRUCTURE-ACTIVITY RELATIONSHIP FOR COMPOUNDS LINKING DMS AND MER-25 (XI)

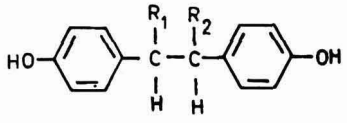
R_1	R_2	R_3	Name of compound	Approx med (μg)		
				Estrogenic (subcutaneous)	Antiestrogenic (intravenous)	Antifertility (subcutaneous/ day)
OH	CH_3	$(C_2H_5)_5$	H-334	1000	6	>1000
OCH_3	CH_3	do	H-336	1000	30	>1000
OCH_3	CH_3	$(C_2H_5)_4$	H-315	>1000	100	>1000
OCH_3	$PhOCH_3$	$(C_2H_5)_2$	H-282	1000	Approx 1000	Approx 100
H	$PhOCH_3$	do	H-286	1000	100	Approx 100
OH	CH_3	do	H-298*	1000	3	Approx 200

*An *erythro*-bibenzyl, not a stilbene derivative, like the rest.

TABLE 11 — STRUCTURE-ACTIVITY RELATIONSHIP FOR DIFFERENT BIBENZYL DERIVATIVES (XII)

R_1	R_2	Substance	Approx med (μg)		
			Estrogenic (subcutaneous)	Antiestrogenic (intravenous)	Antifertility (subcutaneous/ day)
H	CH_3	MHA	>2000	8	>2000
CH_3	do	*meso*-DMA	60	0·3	5
do	do	*dl*-DMA	600	3	100
do	do	*l*-DMA	>1000	3	500
do	do	*d*-DMA*	1000	3	500
do	C_2H_5	*threo*-MEA	1000	1·5	150
do	C_2H_5	*erythro*-MEA	15	0·4	<1
C_2H_5	C_2H_5	*dl*-DEA	80	0·1	10

*Not optically pure.



XII

separation of stereoisomers was sometimes possible, and according to the nature of the compound a member of this series may exist as: (i) a single *dl* pair of optical isomers (MHA); (ii) a *meso*-form and a *dl* pair (DMA); or (iii) two *dl* pairs, the *erythro*- and *threo*-isomers (MEA).

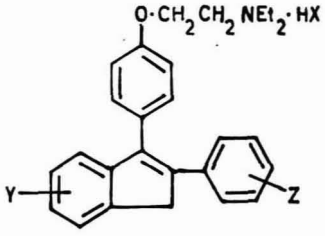
A few typical examples of structure-activity relationship of these compounds are given in Table 11. The compound DMA has been fully resolved, although the *d*-isomer is not yet optically pure; *meso*-DMA is like DMS in estrogenic and antiestrogenic activity, but has 10 times more antifertility potency. The stereoisomers, *d* and *l*-DMA, are much weaker estrogens and antiestrogens than *meso*-DMA, and even still weaker as antifertility agents. Curiously, they have almost equal activity and are somewhat less potent than the *dl* mixture. The compound MEA has, so far, been resolved into the *erythro* and *threo-dl* mixtures. *Erythro*-MEA is almost as potent as estradiol as an antifertility agent, but with about 150th of its potency as an estrogen. Thus, although estrogenic activity is still better correlated in these compounds with antifertility activity than is antiestrogenic activity, there is considerable divergence in the antifertility/ estrogenic ratio as compared to estradiol or diethylstilbestrol.

Erythro-MEA in common with similar bibenzyl and stilbene derivatives is non-toxic in rodents. The therapeutic ratio is of the order of 20,000 in the rat or mouse. Further information about this potent compound will be of considerable interest.

Phloretin[3], like MER-25, is a weak estrogen and possesses antiestrogenic and post-coital antifertility activity in rats. Parahydroxypropiophenone[79] showed some anti-implantation activity in rats, but not in rabbits. A single subcutaneous injection of Vallestril[2] on day 1, 2 or 3 post-coitum prevented implantation in rats. It is interesting that about a quarter of the treated animals remained sterile for 3 months.

The antifertility effect of Clomiphene in rodent species has already been discussed[3,71,72] (Tables 5 and 6). In the present context, its effect on pregnancy in rhesus monkey will be considered[79]. Continuous subcutaneous injection (2·5 mg/kg) every fourth day, or oral administration (40 mg/kg) for 6 days following positive mating did not prevent pregnancy in this species. Prolonged oral medication (40 mg/kg) retarded follicular and luteal development, and caused amenorrhoea. It is worth noting that in rabbits two cases of foetal anomalies have been recorded; obliteration of decidual cells at the implantation sites and degeneration of the endometrial symplasma are other recorded effects of this compound in this animal[79].

The related compound 1-[*p*-(2-diethyl-aminoethoxy)phenyl]-2-(*p*-methoxyphenyl)-1-phenylethane (MRL-37) showed post-coital antifertility activity in rats and mice, possibly through its antideciduoma property related to inherent antiestrogenicity[73,121].

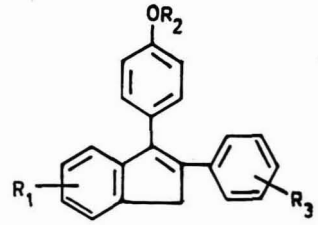


XIII

Lednicer *et al*[124] synthesized 2,3-diphenylindenes (XIII) by partial cyclization of the triphenylethylene structure. The most potent derivative inhibited pregnancy in rodent species (mice, rats, rabbits and guinea-pigs) when given for 7 days (0·5 mg/kg) from proestrus to day 6 post-coitum. Diaryl indenes lacking the basic ether did not show any antifertility activity. Regarding structure-activity relationship, it was found that the presence of a methoxy group at position 6(e) increased the antifertility activity by a factor of 5 as compared to the basic compound (a) or a 5-methoxy derivative (j). The addition of methoxy group at position 5 to compound (e) decreased its potency by a factor of 20 (k). A change in the *para* or *meta* position of the phenyl ring at position 2 did not increase the activity (Table 12).

Of the 2,3-diphenylindene compounds (Tables 5 and 6), U-11555A has been investigated extensively in rodents[71,74,75,79,80]. Its effect on the development and tubal transport of ova has been discussed. Other biologic properties include absence of androgenic, progestational, antigonadotrophic effects, and presence of weak uterotrophic, antideciduomagenic, and antiestrogenic activity at higher doses. In rabbits, apparently a high dose (15 mg/kg) is needed to cause 100% prevention of implantation[79]. The effect on placenta is similar to that described for Clomiphene[79]. This compound is generally non-toxic in rabbits, but produces a skin reaction to sunlight in pigs and human subjects[79].

Lednicer *et al*[147] synthesized more compounds of 2,3-diphenylindene series (XIV) and obtained one with 100% antifertility efficacy in rats when tested by the same procedure in as low a dose as 0·025 mg/rat. Even minor changes in structure had remarkable effect on the antifertility potency of these compounds. Thus, the introduction of a methoxy group at position 5(f) of the parent compound (a) had little effect on the antifertility activity, but a methoxy group at position 6 increased the potency 5 times (Table 13). However, the effect of position 6 is not additive, as the 5,6-dimethoxy compound (l) is less active by a factor of 4 as compared to the unsubstituted parent indene (a). An alteration in the substitution in the phenyl group at position 2 also affects the potency of these compounds. The substitution of a methoxy group in the *para* position of (a) resulted in compound (d) and substitution in the same position in the 6-methoxylated compound (g) gave (k), with no effect on their activity. The introduction of a halogen or methyl group to the basic or 6-methoxylated indenes decreased their activity (b, c, e, i, j). Replacing the diethylamino group of (g) with piperidino (m) or 2,2-dimethylpyrrolidino group (o) had no effect on potency, whereas the morpholino substitution (p) decreased the activity. The incorporation of a pyrrolidino group (n) led to a 4-fold increase in potency.



XIV

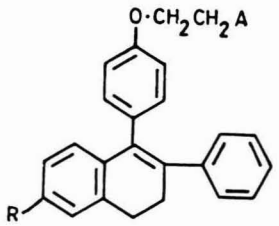
TABLE 12 — STRUCTURE-ACTIVITY RELATIONSHIP FOR 2,3-DIPHENYLINDENES (XIII)

Compound No.	Y	Z	X	MED 100 (mg/kg; 7 days
a	H	H	ClO_4	2·5
e	6-OMe	H	Cl	0·5
j	5-OMe	H	Cl	2·5
k	5,6-diOMe	H	Cl	10·0

TABLE 13 — STRUCTURE-ACTIVITY RELATIONSHIP FOR BASIC ETHERS OF 2,3-DIPHENYLINDENES (XIV)

Compound No.	R_1	R_2	R_3	MED 100 (mg/rat)
a	H	$CH_2CH_2N(C_2H_5)_2$	H	0·5
b	H	do	*p*-F	>2
c	H	do	*p*-CH_3	>2
d	H	do	*p*-OCH_3	0·5
e	H	do	*p*-Cl	>2
f	5-OCH_3	do	H	0·5
g	6-OCH_3	do	H	0·1
h	do	do	*m*-OCH_3	>2
i	do	do	*p*-CH_3	1·0
j	do	do	*p*-Cl	>2
k	do	do	*p*-OCH_3	0·5
l	5,6-diOCH_3	do	H	2·0
m	6-OCH_3	CH_2CH_2-N⬡	H	0·1
n	do	CH_2CH_2-N△	H	0·025
o	do	CH_2CH_2-N⬡	H	0·1
p	do	CH_2CH_2-N⬡-O	H	2·0
q	6-OH	$CH_2CH_2N(C_2H_5)_2$	H	2·0

Lednicer *et al*[126] synthesized related 1,2-diphenyl-3,4-dihydronaphthalenes (XV) and evaluated their post-coital antifertility activity in rat after administration from proestrus to day 6 of pregnancy. As in indenes, the addition of a 6-methoxy group increased the activity and the substitution of pyrrolidino in place of diethylamino group at *para* position of phenyl at 1 increased the activity many times (Table 14).

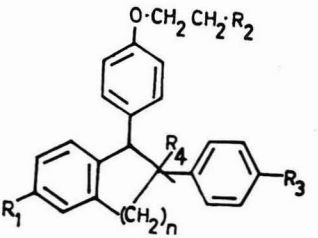


XV

Duncan *et al*[127] investigated two compounds of this series, U-11100A (also *see*[81] Table 9) and 2-[*p*-(3,4-dihydro-6-methoxy-2-phenyl-1-naphthyl)-phenoxy]-triethylamine hydrochloride (U-10520A) for oral antifertility activity in rodents (rats, rabbits and guinea-pigs). The compounds caused 100% inhibition of pregnancy at a dose of 0·025 mg/kg and 0·25 mg/kg, or a single dose of 0·25 mg/kg and 2·5 mg/kg respectively up to day 4 post-coitum. The compounds possess mild uterotrophic, anti-estrogenic and antideciduomagenic activities, but no antigonadotrophic property. In rhesus monkeys[79], oral administration of U-11100A at 25 mg/day for the first 6 days after positive mating had no effect on pregnancy; at 250 mg/day for the same period only partial inhibition of pregnancy was observed. No foetal abnormalities were, however, recorded. The compound was neither blastotoxic nor adversely affected the viability of the blastocysts in rabbits[79].

Lednicer *et al*[128] synthesized more dihydronaphthalenes and tetrahydronaphthols. The naphthalenes were active in rats (proestrus to day 6 of pregnancy) at a dose of 0·005 mg/animal. The compounds showed marked estrogenic activity.

Bencze *et al*[129,130] studied the post-coital antifertility activity of basic phenolic ethers and phenoxyacetic acid derivatives of tetrahydronaphthalenes (XVI). The most active compound was the basic phenolic ether which caused 100% inhibition of pregnancy in rats at an oral dose of 20 μg/kg given on days 1-4 post-coitum. It was slightly uterotrophic and antiestrogenic.



XVI

Regarding structure-activity relationship, the substitution of 6-methoxy group increased the estrogenic, but decreased the anti-implantation potency (20) (Table 15). The same procedure in compound (16) yielded a compound (48) with low activity. Replacement of diethylamino group of compound (16) with pyrrolidino (36), amino (29), or N-ethylamine (31) led to loss of activity. Compound (16) with a chloro group substituted in *para* position of phenyl group at C_2 had greater potency than compounds (10) and (43). The substitution of methyl group in place of hydrogen at C_2 increased

TABLE 14 — STRUCTURE-ACTIVITY RELATIONSHIP FOR 1,2-DIPHENYL-3,4-DIHYDRONAPHTHALENES (XV)

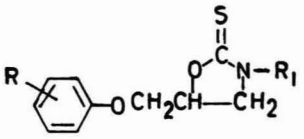
Compound No.	R	A	MED 100 (mg/kg)
a	H	NEt_2	0·5
b	OMe	do	0·25
c	do		0·025
d	do		0·125
e	do		1·0

TABLE 15 — STRUCTURE-ACTIVITY RELATIONSHIP FOR 1,2-DIPHENYL-1,2,3,4-TETRAHYDRONAPHTHALENES (XVI)

Compound No.	R_1	R_2	R_3	R_4	*n*	Uterotrophic activity mg/kg	Antifertility activity mg/kg
10	H	$N(C_2H_5)_2$	H	H	2	2·5	1·0
16	H	do	Cl	do	2	0·04	0·02
20	OCH_3	do	H	do	2	0·002	0·1
29	H	NH_2	Cl	do	2	—	>1·0
31	H	NHC_2H_5	Cl	do	2	—	0·1
36	H	$N(CH_2)_3CH_2$	Cl	do	2	2·5	>0·02
43	H	$N(C_2H_5)_2$	OCH_3	do	2	0·05	1·0
48	OCH_3	do	Cl	do	2	—	0·1
56	H	do	Cl	CH_3	2	0·01	0·04

the uterotrophic activity, but reduced the antifertility activity by about 50%.

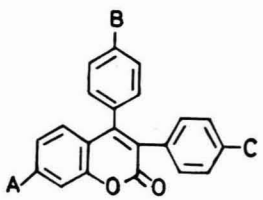
Youngdale *et al*[131] prepared 5-(phenoxymethyl)-2-oxazolidinethiones (XVII). One of the compounds of this series, 5-(α,α,α-trifluro-*m*-tolyoxymethyl)-2-oxazolidinethione (U-11634), caused 100% prevention of implantation in rats after oral or subcutaneous administration for 7 days starting from proestrus at a dose of 2·5 mg/animal. A single dose (10 mg/rat) on days 3-6 post-coitum was equally effective, but it was ineffective on days 1-3. Typical examples of structure-activity relationship are given in Table 16.



XVII

The compound U-11634 is devoid of uterotrophic, antiestrogenic, androgenic and antigonadotrophic properties[132,133]. It inhibits deciduoma formation and blocks progesterone and/or estrogen-induced increase in weight, RNA, protein, glycogen and ^{32}P uptake of the pseudopregnant rat uterus[133]. However, incorporation of tritium into decidual tissue under the influence of steroids was not interrupted. The LD_{50} in mouse was 451 mg/kg (intraperitoneal) and 514 mg/kg (oral) in rats[134]. The compound is apparently non-toxic, non-teratogenic and does not cause photosensitization at the antifertility dose (10 mg/kg). But at higher doses given for a month (30 and 100 mg/kg) it showed slight to moderate toxicity consisting of inhibition of thyroid function and toxic hepatitis. At a still higher dose (300 mg/kg), these effects were severe. Some changes were also recorded in monocyte count and bone marrow. These effects were also seen in dogs. However, the antithyroid and hepatic symptoms were reversed on cessation of treatment. Detailed studies showed that the antifertility activity was not related to the antithyroid effect of the compound.

Lednicer *et al*[135,136] synthesized the basic ethers of 3,4-diphenylcoumarins (XVIII) sterically related to 2,3-diphenylindenes. The most active compound (17) inhibited implantation in rats at an oral dose of 10 mg/animal and compound (13) at a subcutaneous dose of 0·1 mg/animal given for 7 days (proestrus to day 6) (Table 17).



XVIII

Table 16 — Structure-Activity Relationship for 5-(Phenoxymethyl)-2-oxazolidinethiones (XVII)

Compound No.	R	R_1	MED 100 (mg/rat)
37	*o*-CF_3	H	>10
38	*m*-CF_3	H	2·5
39	*m*-CF_3	CH_3	>10

Table 17 — Structure-Activity Relationship for 3,4-Diphenylcoumarins (XVIII)

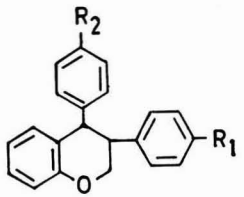
Compound No.	A	B	C	MED 100 (mg/rat)
13	OAC	H	OCH_3	0·1
14	OAC	H	H	0·1
17	OH	H	OCH_3	10 (oral)
19	H	$OCH_2CH_2N(C_2H_5)_2$	OCH_3	>10

Table 18 — Structure-Activity Relationship for *trans*-3,4-Diphenylchromanes (XIX)

Compound No.	R_1	R_2	MED 100 (mg/kg)
15	H	$OCH_2CH_2N(C_2H_5)_2$	>1·0
16	H	OCH_2CH_2N	>1·0
18	Cl	$OCH_2CH_2N(C_2H_5)_2$	1·0

The indene corresponding to compound (19) was active at a dose of 0·5 mg/rat. It may be interesting to prepare a compound with methoxy substitution at A and pyrrolidine at B, since these groupings enhanced considerably the antifertility potency in indenes and naphthalenes.

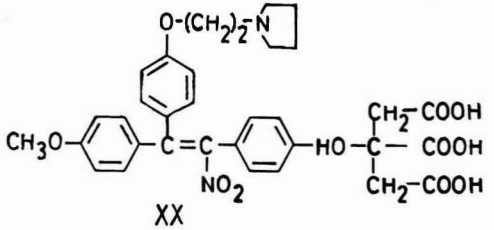
Carney *et al*[148] investigated *trans*-3,4-diphenylchromanes (XIX) for post-coital antifertility activity in rats. But only compound (18) was effective at a dose of 1 mg/kg given on days 1-4 post-coitum (Table 18).



XIX

ORF-3858[79] showed potent post-coital oral antifertility activity in rabbits. It is non-toxic and non-teratogenic. Studies conducted in rhesus monkeys showed that administration by the same route (10 mg) for 6 days post-coitum prevented implantation without any effect on the menstrual cycle. It is a highly promising compound and deserves clinical trial.

A nitrostyryl compound, 1-[2-{*p*-α-(*p*-methoxyphenyl) - β - nitrostyryl} - phenoxy] - ethylpyrrolidine monocitrate (CN-55945-27)[137] (XX) has been reported to exert antifertility effect in mice (50 μg/kg), rats (25 μg/kg) and dogs (250-500 μg/kg) when fed continuously in diet. A single dose (500 μg/kg) administered on day 1, 2 or 3 post-coitum prevented implantation in rats and mice. It has weak uterotrophic, antiestrogenic and antideciduomagenic activities. LD_{50} in mice is 832 ± 32 mg/kg, and in rats 1778 ± 53 mg/kg. The compound is apparently non-teratogenic.



XX

Callantine *et al*[138] carried out detailed biologic studies with CN-55945-27. In addition to the properties mentioned above[137], they observed that the compound stimulated pituitary LH secretion, but had no effect on FSH. Prolonged treatment (<14 days) had no effect on pituitary LH activity. Another interesting property of this compound is its marked inhibitory effect on uterine motility *in vitro*. Callantine *et al*[138] concluded that the compound exerts its anti-implantation effect through its antiestrogenicity and/or luteolytic action via LH. It is yet another promising anti-implantation agent.

Gopalachari and Iyer[139] prepared 7-methoxy-4-(*p*-β-pyrrolidinoethoxy)-phenyl-isoflaven-4-ol and found it to be an effective antifertility agent in rats when given orally (5 mg/kg) on days 1-5 post-coitum. Moersch *et al*[140] investigated the anti-implantation effect of isoflavones related to genistein. Only 2 compounds out of a series of 47 gave positive results in rats (10 mg/kg, days 1-4 post-coitum).

A series of 2,3-diphenylindole and related compounds were synthesized by Landquist and Marsden[141] and Iyer and Gopalachari[142]. Of these, the most active compounds were: (i) 5-fluoro-3-phenyl-2-*p*-(β-pyrrolidinoethoxy)-phenylindole, and (ii) 3-phenyl-2-*p*-(β-pyrrolidinoethoxy)-phenylindole, which cause 100% prevention of implantation in rats when given orally (10 mg/kg) on days 1-5 post-coitum[143].

A series of basic ethers of 2,3-diphenylacrylophenones were synthesized and evaluated for post-coital antifertility activity in rats[144]. The most potent compound was 2-*p*-chlorophenyl-2-phenyl-4-β-pyrrolidinoethoxy-acrylophenone, which prevented implantation after oral administration (1 mg/kg) on days 1-5 post-coitum.

Kamboj and Kar[145] investigated the anti-implantation effect of several aromatic sulphur derivatives. The most potent of these was *p,p'*-diaminodiphenylsulphide, which caused 100% inhibition of implantation in rats when given orally (100 mg/kg) on days 1-5 post-coitum. Lower doses reduced the number of implantations by about 50%.

Compound 66/179 has been studied extensively for oral antifertility activity in rodents and rhesus monkeys (Kar, A. B., Kamboj, V. P., Setty, B. S. & Chandra, H., unpublished data). It caused 100% reduction of implantation in rats (med 2 mg/kg) in days 1-5 post-coitum regime, or at a single dose (med 10 mg/kg) administered on day 1, 2, 3 or 4 of pregnancy. In mice a single feeding (10 mg/kg) on day 1, 2 or 3 post-coitum was similarly effective, but this procedure was ineffective in rabbits. In 10 rhesus monkeys a single oral dose (10 mg/kg) 24 hr after positive mating prevented pregnancy. The compound has no effect on the menstrual cycle in this species. It exerts uterotrophic effect in immature rhesus monkeys, but no particular change is noticed in the sex skin or breasts. Other biologic features in rats (and rabbits) include mild uterotrophic activity, antiprogestational effect in delayed implantation but not in Clauberg assay, and antideciduomagenic property. It is not blastotoxic and does not interfere with fertilization, development and tubal transport of ova.

The LD_{50} of compound 66/179 in mice (intraperitoneal) is 400 mg/kg. It is devoid of pharmacologic activity except partial α-adrenergic blockade at higher doses. No gross toxic symptoms were found in female rhesus monkeys fed with the compound (10 mg/kg) 9 times/month for 3 months.

Coppola and Ball[149] studied the post-coital antifertility effect of U-11555A and Clomiphene after topical application. The compounds were suspended in a vanishing cream base and applied in a volume of 0·01 ml to a shaved area on the back. It was observed that daily application (med: U-11555A — 1 mg/kg; Clomiphene — 0·1 mg/kg) on days 1-5 post-coitum, or a single application (med: U-11555A — 10 mg/kg; Clomiphene — 1 mg/kg) on day 1 prevented implantation completely. Apparently, Clomiphene was more potent than U-11555A. Since the former has also been reported to induce ovulation in women[3], it will be interesting to explore whether this can be achieved by topical application in a suitable vanishing cream base.

Kar *et al*[150] reported that several estrogenic (estrone, estradiol-17β, 3-cyclopentyl ether of 17α-ethyl estradiol) and progestational steroids (Norethynodrel, ethynodiol diacetate), and non-steroidal compounds (diethylstilbestrol, DBF[84], 66/179) caused 100% prevention of implantation in rats after percutaneous application in alcoholic solution. A single application on day 1 post-coitum (except DBF) or daily application on days 1-5 was equally effective. Earlier, Shipley[151] and Ringler[152] demonstrated antiovulatory effect of several progestational steroids in rabbits when applied topically. This technique merits further exploration from practical contraception standpoint.

Currently, considerable attention is paid to the mechanism of anti-implantation action of antiestrogens. The problem is most complex and there is much diversity of opinion. The present position has been reviewed exhaustively by Prasad and Kalra[125]. On the basis of biologic profile of the different antiestrogenic compounds (vaginal smear

and uterotrophic response; inhibition of uptake of labelled estrogen, decidual cell reaction, and estrogen-induced physiologic processes; antifertility effect exerted at tubal or uterine level; blastotoxicity; and effect on blastocysts in delayed implantation), their anti-implantation action is considered to be due to one or more of the following mechanisms: (i) the compounds may increase tubal and uterine motility (by their uterotrophic or proestrogenic activity) resulting in expulsion of ova and blastocysts (DMS, MER-25, Clomiphene, U-11100A, U-11555A, DBF); (ii) the compounds may be cytotoxic and affect the viability of ova and blastocysts (MER-25); (iii) they may inhibit the uptake of estrogen by the uterus and interfere with decidualization (MER-25, Clomiphene, U-11555A, CN-55945-27, 66/179); (iv) by their antihistaminic activity they may inhibit estrogen-induced histamine action on the uterus and subsequent decidualization (Clomiphene, U-11555A, U-11100A); (v) they may inhibit decidual cell response by blocking estrogen-dependent enzyme activities (MER-25) or estrogen-dependent nucleoprotein synthesis (U-11634); and (vi) the compound may cause luteolysis through a stimulation of pituitary LH secretion; the lowered progesterone level may then interfere with implantation (CN-55945-27).

It is important to realize that the mechanisms suggested above may be valid mainly for rats which require estrogen for implantation. In a species such as hamster in which estrogen is not critical for this process, U-11100A, U-11555A and U-11634 have been found to be ineffective in preventing implantation[125]. To add to the complexity of the problem, U-11100A has only partial post-coital antifertility activity in rhesus monkeys[79], but another antiestrogenic compound (66/179) shows this effect fully in the same species[146]. The *modus operandi* of the latter is, however, unknown and so is the nature of hormonal mechanisms responsible for implantation in primates. The importance of knowledge on implantation mechanisms in primates and its bearing on the development of effective post-coital antifertility agents can hardly be overestimated.

Abortifacient Agents

Only limited coverage is given here to agents which cause resorption or abortion of the implanted embryos. Many of the cytotoxic agents (antimitotics, antimetabolites) listed in Table 5 as ova poisons, also cause foetal destruction when given after implantation. Robson[153] reviewed the relevant literature and pointed out the distinction between the direct foetal effects, and effects secondary to the general toxicity of these agents after systemic administration.

Thiersch[154] has reviewed his earlier work on the abortifacient effect of antimetabolites, and reported some of his more recent results indicating quite favourable therapeutic ratios for some of the compounds — 6-thioguanine, 6-(1-CH_3-4′-nitro-5′-imidazolyl)-mercaptopurine and 6-(2′,4′-dinitrophenyl)-mercaptopurine[66,155,156].

Interference with established pregnancy in rat by 5-hydroxy tryptamine[94] and certain antihistaminics[157] seems to be due to a disturbance in placental blood flow. Methylcholanthrene and contact insecticides (thiophosphonic ester, hexachlorocyclohexane) have been found to cause foetal destruction in rats and mice[1].

Paragyline hydrochloride (Eutonyl), a monoamine oxidase inhibitor, has been reported to cause abortion in 16/20 women when injected directly into the amniotic sac in a single dose of 50-100 mg in 20 ml normal saline during week 10-20 of pregnancy[158]. Similar effects of the compound have been reported earlier in rats[159].

Considerable attention has been paid to the abortifacient activity of 6-azauridine by Raskova, Elis and their associates[160] following the early report of Sanders *et al*[161]. However, in a recent clinical study[160], the compound was administered intravenously in single doses (7·5-15 g) to pregnant women. Pregnancies of 1·5-2·5 months' duration were interrupted 1-8 days post-treatment. In 10 cases diffuse micromolar degeneration and in 1 case focal degeneration of the chorion were observed. In 4 cases there was marked proliferation of trophoblastic syncitial lamellae. It was concluded that 6-azauridine has a definite deleterious effect on early pregnancy.

A synthetic analogue of cytidine, 6-azacytidine, has been shown to interrupt pregnancy in mice during the first 7 days[162].

Much interest is created by the recent report about the 'Swedish pill', which is an unsymmetrical diphenylethylene derivative (F6103)[163-165]. It is claimed to terminate pregnancy in women no later than a month after conception with 100% success. The compound accumulates in the corpora luteum and antagonizes progesterone action. It has mild estrogenic but potent pituitary gonadotrophin-inhibiting properties in animals and post-menopausal women[165]. However, any prospect of practical application of this compound is as yet uncertain[166,167].

Discussion

From a critical consideration of the vast number of non-steroidal compounds interfering with different phases of reproduction in the female, attention is drawn to the fact that only a few of them have been investigated in women and undergone thorough contraceptive evaluation. Diethylstilbestrol[11,123], *m*-xylohydroquinone[98] and, to a limited extent, ergocornine[103] and F6103[163] are perhaps the only exceptions. The systematic use of infra-human primate species, such as the rhesus monkey, in contraceptive trial studies with potential antifertility agents has just begun[66,79,84] (also Kar, A. B., Kamboj, V. P., Setty, B. S. & Chandra, H., unpublished data) and is expected to be extended more universally. The desirability and importance of this procedure are too obvious to merit further elaboration. Indeed, according to Morris and van Wagenen[123], 'success in the macaque should be paralleled by success in man'.

All the 3 compounds reported to block ovulation in women are inhibitors of pituitary gonadotrophin: diethylstilbestrol[11,12,29] and F6066[25] apparently achieve this through their inherent estrogenicity. Whether the same is true of Methallibure[20] is not

known, although its post-coital antifertility efficacy in rats[76] would point towards such a possibility. Diethylstilbestrol is a promising compound and deserves further clinical trial as an oral contraceptive. It may be particularly interesting to formulate a contraceptive dose regime at which the compound would interfere only with the peripheral action of gonadotrophin[12], rather than working via the intricate CNS mechanisms. Such a dose regime dissociating peripheral from the central effects of a gonadotrophin inhibitor has been actually demonstrated in the case of Methallibure[29]. F6066[25] is yet another interesting compound and its contraceptive trial in women is indicated.

To inhibit ovulation, diethylstilbestrol and F6066 generally require a rather long-drawn and rigid schedule, which may not always be convenient for the unsophisticated masses. Accordingly, there is a good case for the development of compounds with more protracted action, so that ovulation inhibition may be achieved with infrequent doses.

Such simplicity of the regimen is perhaps an important factor in the current interest in the development of post-coital or post-ovulatory antifertility agents. There seems to be little doubt that a safe and 100% effective 'after-the-act' pill will be a positive addition to the armoury of the existing contraceptive techniques.

Extensive animal studies during the last 8 years have established that it is possible to prevent conception after ovulation by a variety of non-steroidal agents. Particularly illuminating has been the organized synthesis of potential post-coital antifertility compounds, their bio-evaluation and structure-activity relationship studies. This, together with the mounting body of physiologic information on fertilization, zygotic development and transport, and the implantation process, could be expected to provide leads for more rational synthesis of newer post-coitally effective antifertility agents. A breakthrough in the near future is not a too optimistic guess.

Of the existing post-coital compounds, diethylstilbestrol[123], ORF-3858[123], U-10293[99], *erythro*-MEA[122], CN-55945-27[140] and 66/179 (Kar, A. B., Kamboj, V. P., Setty, B. S. & Chandra, H., unpublished data) appear to be promising. Diethylstilbestrol, ORF-3885 and 66/179 are particularly noteworthy, since they have proved effective in women and/or in rhesus monkeys. Diethylstilbestrol has some prospect of routine use as a post-coital pill.

Summary

The current status of non-steroidal compounds reported to interfere with ovulation, development and tubal transport of ova, implantation and established pregnancy has been reviewed in detail. The chemistry, structure-activity relationship, biologic profile, *modus operandi*, and the results of human trials, wherever available, have been considered critically. An attempt has been made to assess the prospects of these different categories of compounds for routine use as oral contraceptives by women. It is concluded that some of the anti-implantation agents are expected to find practical application, and would be valuable additions to the armoury of the existing techniques for birth control and family planning.

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REVIEWS

GEOMETRY OF QUANTUM THEORY, Vol I, by V. S. Varadarajan (D. Van Nostrand Co Inc, Princeton), 1968. Pp xiv+193. Price $ 8.50

The book deals with a mathematical analysis of the axioms of quantum mechanics. The basic idea is that every physical system may be associated with a certain ortho-complemented lattice (called the logic of the system) whose elements are experimentally verifiable propositions about the system. For classical systems this lattice is a Boolean algebra and for quantum mechanical systems it is non-distributive. A brief outline of the contents follows. This volume is divided into seven chapters, the first five are marked out as part one and the remaining two as part two. Chapter one deals with Boolean algebras and their realizations. Chapter two describes complemented modular lattices and finite dimensional projective geometries and their realization as lattices of linear manifolds of a finite dimensional vector space over a division ring. The theory of these geometries is studied in chapters three and four. Isomorphisms and ortho-complementation are introduced in such geometries by semi-linear transformations and semi-bilinear transformations. Chapter five leads to the theorem that a geometry of rank greater than or equal to four is isomorphic to the lattice of all finite dimensional sub-spaces of a vector space over a division ring. In chapter six observables and states associated with a logic are given and the probability distribution of an observable in a state is described. In the last chapter the notion of standard logics is introduced and the representation of observables as self-adjoint operates and pure states as rays of a suitable Hilbert space are discussed.

The topics dealt with in the book are interesting, but the presentation of the material is defective in several respects. The notation in the opening chapter is not adequately explained and the material is not properly arranged. Some of the definitions of even standard terms given in the book are not sharp and the proofs given are round about. The space dealt with for describing the structures of classical systems is disproportionately large and the main topic, namely the geometry of quantum mechanics, dealt with in the last two chapters is mostly speculative. On the whole, one gets the impression that the book is still in the form of lecture notes rather than a systematic presentation of a unified topic.

T. VENKATARAYUDU

DIFFUSION KINETICS FOR ATOMS IN CRYSTALS by J. R. Manning (D. Van Nostrand Co Inc, New York), 1968. Pp xv+257. Price $ 9.75

This probably is the first systematic attempt at describing the theory of diffusion of point defects in crystalline substances. The central theme on which the discussion is based is ' random walk '. Diffusion, being not only of theoretical but also of technical importance, has always received the attention it deserves. Seldom, however, has it been thoroughly discussed from an atomic viewpoint as in this book. The need for a book of this kind has long been felt, but the present is parhaps the most opportune time for its appearance.

The book starts with a brief description of postulated mechanisms which are essential to any theory of diffusion. After an exposition of the basic concepts (including Fick's laws) in the first chapter, the book deals with random walk diffusion and correlation effects (in the absence or presence of a driving force) in the next three chapters. It then deals with problems of variable diffusion coefficient and of non-equilibrium situations. It concludes with a brief account of more specialized applications.

The material is carefully selected and admirably edited. A good deal of the discussion is original, some published for the first time. A book on a subject which draws on and contributes to a wide variety of scientific disciplines must suffer from some drawbacks, but this one suffers from only a few. The multitude of symbols and definitions will undoubtedly bewilder and deter a first reader — who, therefore, must turn to less formal accounts as a beginning. Comparison with experimental results is paid less attention than it should be. An example is: "...Experiments on magnetic resonance can yield valuable information on jump frequencies...". The experimental scientist may tend, as quickly as possible, to turn to the last chapter (Other applications) wherein he will find some information on how to establish the diffusion mechanism in the particular crystals he is working with. An author index would have been useful.

As far as the reviewer can see, there is something in this book for everybody: Formal theory for the mathematically minded, discussion of basic mechanisms for the experimenter, and indication of the use of the results for the working metallurgist.

A. S. PARASNIS

ADVANCED ORGANIC CHEMISTRY: REACTIONS, MECHANISMS AND STRUCTURE by Jerry March (McGraw-Hill Book Co Inc, New York), 1968. Pp xiv+1098. Price $ 16.75

This book is divided into two parts. The first portion, comprising nine chapters, covers fundamental concepts of chemical bonding, structure stereochemistry and reaction mechanisms. The level of discussion is fairly advanced but is within easy grasp of a graduate student. Wherever necessary, lucid diagrams and illustrations are incorporated. For those interested in detailed treatment of specialized topics copious references to reviews, key articles and books have been appended. Instrumental methods for determination of structure, however, are covered in a chapter of 32 pages only. In the opinion of the reviewer this subject merits more space in a book on ' Reactions, mechanisms and structure '.

In the second part, organic reactions are dealt with. Their division is primarily based on reaction types and not mechanisms; substitution, addition to multiple bonds, elimination, rearrangement and oxidation-reduction constitute the major types. Each chapter is subdivided into two sections. In the first section, the various mechanisms met with in the particular category are discussed. This is followed by general considerations of orientation and reactivity. In the second section, individual reactions falling in the class indicated in the title of the chapter are covered. Each reaction is allotted a numbered subsection. Its scope and utility are discussed and special mechanistic features are pointed out. At the end is given a list of all organic synthesis references to that reaction. This novel feature increases the practical value of the volume considerably. Altogether about 500 reactions are dealt with. Omission of photochemical reactions seems somewhat arbitrary, otherwise the coverage is compendious and refreshingly up to date.

The appendix section has some interesting notes on the naming of organic compounds and literature searching. Also given is a reclassification of the reactions based on the type of compound synthesized, with back references to the main text.

The book is primarily written for graduate students but is of unquestionable utility to practising organic chemists also. Perhaps as a consequence of tremendous development in this field, a number of books on modern organic chemistry have recently appeared in the market. Many of these cover the subject adequately. The present volume has the additional merit of extensive references which are easy to locate due to its distinctive organization.

S. V. KESSAR

ORGANIC REACTIONS: Vol 16 — THE ALDOL CONDENSATION by A. T. Nielsen & W. J. Houlihan (John Wiley & Sons Inc, New York), 1968. Price $ 15.95

Unlike earlier volumes, Volume 16 covers a single reaction. This arrangement is fully justified when one considers the very wide scope of the aldol condensation, which includes all reactions leading to β-hydroxyaldehydes or β-hydroxyketones and their dehydration products. However, the discussion of the aldol condensation occupies only 85 pages; the remaining 353 pages consist of 20 tables and 2359 references. There is no subject index. The volume, therefore, is not easy to use, even for reference purposes, and it is difficult to see the purpose of such an exhaustive tabulation. Although all the important aspects of the aldol condensation are discussed clearly and competently, the book suffers from the compression of extensive data into too little space. Our knowledge of the stereochemistry of the aldol condensation is admittedly limited, but the available information is outlined all too briefly. The ' Robinson annelation reaction ' is referred to in connection with stereochemistry, but this synthesis of bicyclic unsaturated ketones, in which a crucial cyclization is effected by means of an aldol condensation, merits much fuller treatment in this volume.

K.V.

THE CARCINOGENIC ACTION OF MINERAL OILS: A CHEMICAL AND BIOLOGICAL STUDY (Her Majesty's Stationery Office, London), 1968. Pp xii+251. Price £ 2

This monograph, forming the Medical Research Council Special Report No. 306, deals with exhaustive isolation and identification of constituents of crude oils from Kuwait, Oklahoma and Lagunillas. Biological testing of each of these fractions for carcinogenic activity is reported. No potent carcinogens have been found, but the presence of compounds related to known polycyclic aromatic carcinogens has been established. The combined action of these closely related components is implicated in the carcinogenic activity of the crude oils. This book is recommended as a reference book for all those dealing with public health problems, mineral oils and industrial carcinogens.

M. B. SAHASRABUDHE

SELECTED PAPERS ON DESALINATION AND OCEAN TECHNOLOGY edited by Sumner N. Levine (Dover Publications Inc, New York), 1968. Pp viii +437

The publication under review contains 24 selected papers on the general technology and economics of various techniques employed for water conversion both for providing potable water and for the recovery of chemicals.

Desalination is gaining ground since increased demands for water requirement have to be met and natural sweet water resources are dwindling. This problem is universal in nature and the conferences held periodically all over the world have brought home the measures being adopted to solve this important problem.

The papers compiled in this publication have already been published in different journals, symposia proceedings, etc, and the author has pointed out that this publication was expected to ' provide a background reading in desalination and related aspects of chemical oceanography ' and this it has amply fulfilled.

Papers on flash evaporation technique, electrodialysis, use of nuclear heat source, falling film process, reverse osmosis and freezing process have been selected from published literature. Operating experience with installed flash distillation plants, submerged tube type sea water evaporators and electrodialysis plants is described in different papers.

In order to compare the various techniques, papers on the technology of sea water desalination, thermoeconomics of saline water conversion and economic boundaries of saline water conversion have been included along with a standardized procedure for estimating costs of saline water conversion.

The important aspect of corrosion and scale prevention in equipment used for desalination has been covered in articles where the fundamental factors affecting corrosion of metals in water have been considered and a critical review is provided on the formation and prevention of scale. Methods for scale control in flash systems are indicated.

As a direct consequence of desalination of sea and brackish waters, it is anticipated that potential

sources for the recovery of chemicals will be found in the concentrated residues. Recovery of these byproducts has been considered and a review is presented of the methods suggested for mineral recovery. The possibility of recovering essential minerals from the sea has been presented in a paper where the sea is considered as a source of dissolved chemicals.

Grouping together of published data in an easily available form makes this compilation valuable to the scientists, engineers and to those interested in the implementation of scientific findings in this field. Since details on practical experience gained with different techniques are also included, the book will serve as a valuable guide to skilled operators of treatment plants.

The author and the publishers are to be congratulated for the timely compilation of this low-priced publication which will be of great help to those engaged in studies on desalination.

N. KRISHNASWAMY

GEOLOGY OF INDIA by A. K. Dey (National Book Trust, New Delhi), 1968. Pp xi+178. Price Rs 5.25

This book is intended to make available the factual knowledge regarding geology of India to the average educated reader who is not a specialist. Chapters I-IV, pages 1-44, present a summary of general geology, mineralogy, petrology, structural geology, stratigraphy and palaeontology. The important minerals and main rocks, belonging to the igneous, sedimentary and metamorphic classes are described. How a simple geological map is prepared in the field by a geologist is indicated. An attempt is made to explain the origin of mountains by the theories of isostasy and geosynclines. Fossils are described in detail and geological time scale is explained with the help of a chart.

Chapters V-XVII, pages 45-167, deal with the geological history of India and its economic mineral resources. The Dharwars, Aravallis, Eastern Ghats, Cuddapahs and Vindhyans are described with an attempt to illustrate how they were formed hundreds of millions of years ago. Occurrence of iron, manganese, chromium and other ores, and minerals in them is noted. The Palaeozoic, the Gondwana and the Mesozoic stratigraphy are described and their relation to the stratigraphy of the neighbouring southern content is suggested. Several maps of India are drawn showing the seas in which the sediments were deposited during past geological periods. Trilobites, Graptolites, Brachiopods, Corals, Crinoids, Cephalopods and Reptiles, buried in these deposits, are described. The deposition of the sediments in the Tethy's Basin and how the Himalayas rose in various stages from this site are indicated. Foraminifera and Mammals buried in these deposits are described and the evolution of man treated in detail.

The author has summarized in the course of the first 44 pages what is written in several elementary and advanced text-books. He has illustrated the minerals with excellent coloured photographs (Figs. 1a-1d) and rocks with very good photographs (Figs. 2a-2d and 3a-3d). The fossils are described with the help of good evolution charts (Figs. 5a-5c). The description of Mammals and the evolution of the man is ably dealt with. A mineral resources map and a geological map of India (Maps 1 and 2) are of help to the average reader.

The author has taken up an uphill task to summarize several branches of geology in the first 44 pages and made statements such as " the interior of earth, however, need not be liquid " (p 4) — evidence of liquid interior exists; " minerals have a definite chemical composition " (p 5) — instead of definite composition or definite range in chemical composition; and " amphiboles of which hornblende is common, are hydrous " (p 6) — instead of hydroxyl bearing. The reader should not, however, get away with the impression that the topics are as simple as they may appear after reading these pages. The author could have perhaps laid more stress on actual data on the lithology, structure and life rather than reconstruction of palaeogeography of each period on the basis of continental drift which may be more appropriate in an advanced text. It is, however, good to remember that not all geologists subscribe to the theory of continental drift, though the theory seems to suggest a solution to the stratigraphic problems of this vast region. Moreover, for a general book of this nature, the treatment of Cainozoic era could have been less. In this part, some of the statements made, such as Fig. 15 " Earth's surface when the first seas were formed " (p 50) — appear to be purely on speculation. For the statement " these geosynclines gave birth to many generations of mountain ranges " (p 50) — no explanation is provided. The author says: " disturbance and dislocation of earth's crust which resulted in the extinction of the dinosaurs " (p 110) — however, the causes of extinction of the dinosaurs are different.

However, in view of the very few books written on ' Geology of India ' (this book is about the fifth) and in view of very good illustrations of minerals, rocks and fossils, the book is recommended for a non-specialist reader.

A. SRIRAMADAS

PUBLICATIONS RECEIVED

PRACTICAL POLAROGRAPHY by J. Heyrovsky & P. Zuman (Academic Press Inc, London), 1968. Pp viii+237. Price 50*s*

NMR BAND HANDBOOK by Herman A. Szymanski & Robert E. Yelin (IFI/Plenum Press, New York), 1968. Pp xvi+432

INTERNATIONAL CONFERENCE ON SPECTROSCOPY, JANUARY 1967, BOMBAY (Department of Atomic Energy, Government of India), 1968. Pp x+288. Price Rs 75.00

THE FRAMEWORK OF TECHNICAL INNOVATION by S. A. J. Parson (Macmillan & Co Ltd, London), 1968. Pp x+196. Price 42*s*

RESEARCH IN PROGRESS, Vol 1 — PHYSICAL SCIENCES (Interuniversity Board of India and Ceylon, New Delhi), 1968. Pp xvi+429. Price Rs 40.00

NOTES & NEWS

Centre of Advanced Study in Biochemistry, Bangalore

The Department of Biochemistry, Indian Institute of Science, Bangalore, has been recognized by the University Grants Commission as a Centre of Advanced Study. The University Grants Commission will provide the Centre Rs 1·3 lakhs per annum as recurring and Rs 6·5 lakhs as non-recurring grants for this purpose.

The Department of Biochemistry, established in 1921, is one of the oldest departments in this discipline in the country and has been a leading centre for post-graduate training and research. It has evolved a distinct character in its programme of work, striving always towards maintaining highest possible standards and has earned international recognition. The Department imparts specialized training and conducts original investigations in different branches of biochemistry and functions as an all-India institute attracting the best students from all over the country. The large number of research schemes sponsored by national and international agencies provide valuable opportunity for the staff to contribute to the solution of applied problems of national interest and to maintain active scientific collaboration with other organizations, research institutes and universities.

The Department of Biochemistry is well equipped for biochemical work, having such special apparatus as high speed refrigerated centrifuges, analytical ultracentrifuge, automatic amino acid analyser, electrophoresis apparatus, freeze drying equipment, fraction collectors, spectrophotometers, etc. Facilities also exist for fundamental biochemical investigations by the use of radioactive isotopes. During the last 10 years, in the Department's well-equipped laboratories, 110 research workers received training and about 390 publications appeared in national and international journals. The Department also possesses one of the finest libraries in the field of biochemistry and subscribes to as many as 150 research journals.

The major areas of biochemistry in which the Department has made significant contributions in past years and in which work is in progress are: (i) lipid and vitamin metabolism, (ii) proteins, (iii) plant biochemistry, (iv) endocrine biochemistry, (v) nucleic acids, (vi) antibiotics and chemotherapy, (vii) sanitation biochemistry and (viii) cytogenetics. The specific problems under investigation by a research staff of 3 professors, 9 assistant professors, 3 lecturers and 65 research workers are as follows: (1) interrelationship among vitamins, metabolism of trace elements and proteins, (2) biochemistry of carotenoids and vitamins, (3) nutritional studies with proteins, (4) cytogenetics of yeast and other micro-organisms, (5) cytology of excised root, calli and cell cultures, (6) antibiotics and chemotherapy, with special reference to viruses, (7) treatment and utilization of sewage and industrial wastes, (8) lipid metabolism, (9) nucleic acid metabolism, (10) quinones and oxidative metabolism, (11) nitrogen metabolism in plants, (12) relationship between structure of protein and its function, (13) plant tumour studies, and (14) studies on reproductive biology. The Department proposes to carry out extensive investigations during the next five years in the area of protein, lipid and vitamin metabolism along with the closely related areas of plant biochemistry, endocrine biochemistry and nucleic acids.

The University Grants Commission, while recognizing the Biochemistry Department as a Centre of Advanced Study, has emphasized that the Department, with all its well-qualified staff and exceedingly good laboratory facilities for advanced training and research in the subject, should undertake some organized teaching at the M.Sc. and post-M.Sc. levels. Such organized teaching and enrolment of post-graduate students would be of mutual advantage in that the staff of the Department would come in contact with fresh young minds and would be able to train them in a suitable way for taking up teaching and research positions. It has also been emphasized that one of the essential functions of a Centre of Advanced Study is to engage itself in advanced teaching and research, as otherwise there is the danger of the Centre becoming purely a research institution making no impact on the universities in the country.

The Department of Biochemistry, Indian Institute of Science, occupies a premier position in the teaching of and research in biochemistry and its recognition as a national centre for advanced training and research in the field of biochemistry is a fitting tribute to the high standards and excellence in training and research activities of the institution.

Gunn effect and miniaturization of microwave transmitters

A breakthrough in the frontier of communications technology can be expected with the prospective miniaturization of microwave transmitters based on the 'Gunn effect' discovered by Dr Ian Gunn of IBM in 1963. As a consequence, the currently used bulky and costly high frequency oscillators involving the use of microwave power could be considerably reduced in size. Notable among the possibilities that this development opens up are: (1) personalized radar, to be used by the blind or by the hunters, or as navigation aids for small craft and pleasure boats; (2) combined radio and television, enabling communication with all parts of the world for the cost of a phone call; (3) commercial radio-telephone links in remote areas where present heavy equipment cannot be transported; and (4) lightweight microwave transmitters for communication with spacecraft. The last facility is already in the experimental stage at the laboratories of the National Aeronautics & Space Administration, USA.

Dr Gunn discovered the peculiar behaviour of electrons in gallium

arsenide (GaAs) when a field of about 2000 V/cm was maintained across the semiconductor. The free electrons in the solid gallium arsenide get excited and begin to move with increasing energy until they attain the maximum value of the energy band which they occupy as permitted by the laws of quantum mechanics. Beyond this limit, further gain of energy by the electrons makes them sluggish, as if their effective masses have increased. When these sluggish electrons jump to the higher energy band, the slowdown of the movement of the electrons becomes abruptly so great that the current starts to drop. If the voltage is held constant, these electrons in the higher band are liable to lose energy by collision or radiation, as a result of which they fall back to the lower energy band. Thus, a cyclic movement of electrons between the upper and lower bands is made possible.

The sluggish electrons tend to form clumps and they propagate as a kind of electrical shock wave from the cathode to the anode. The shock wave results in a depression of current in the conductor and when the shock has reached the anode, the current returns to the expected value until a new shock wave forms at the cathode. The net effect is a rhythmic fluctuation of current.

The frequency characteristics of gallium arsenide could be so arranged as to make the electron jump in and out of the high energy band quick enough to avoid the formation of clumps and thus make all the available electrons to participate in raising and lowering the current. In principle, it is possible to obtain any power by making use of GaAs oscillator of a suitable size. Much work is currently being done in the practical realization of higher and higher powers.

Some devices based on the Gunn effect are already in the development stage. At the Electronics Research Centre of NASA at Cambridge, Mass., transmitters and receivers have been fabricated which are small enough to be held in the palm of the hand, but which can send a signal from Cambridge to Boston, a mile away. So far, experimental devices yield a maximum of $\frac{1}{2}$ W of continuous power. It is, however, expected that a quarter of a million watts of pulse power at 10,000 c/s could be generated from a 1 g piece of GaAs. The attainment of this depends on further advancement of materials technology in respect of GaAs [*Sci. News*, **94** (No. 5) (1968), 116].

Method for mapping gene deletions on chromosomes

Electron microscope pictures of DNA molecules from specially prepared λ-bacteriophage are used in a method for mapping the position of genetic deletions on the chromosome developed by R. W. Davis and N. Davidson of the California Institute of Technology. A mixture of DNA from wild type and mutant phages is dissociated into single strands and then re-annealed to form duplex molecules again. The mixture now contains some heteroduplex molecules consisting of a wild type and a mutant strand. When the mixture is examined in the electron microscope, the position of deletions in the mutant molecule is seen where 'bushes' of single strand wild type DNA are left unpaired. The position of genetic deletions can be mapped relative to each other and to the ends of the chromosome. Study of the 'bush' itself shows whether the deletion is a simple one or perhaps involves substitution of a partially homologous piece of DNA [*Sci. J.*, **4** (11) (1968), 5].

Production of food by plants without light

The success achieved by a team of scientist at the Physical Research Centre, TRW Systems Group, California, in producing food and oxygen without the need of light marks a big advance in the direction of artificial plant synthesis as a substitute for the normal photosynthesis reaction. In these studies, electrochemical energy was used in place of photochemical energy for producing carbohydrates from green plant extracts.

The key to the success has been the discovery of a new way of converting triphosphopyridine nucleotide (TPN*) to its reduced form (TPNH). In the photosynthetic pathway, this conversion, involving transfer of electrons, is accomplished through the use of light energy. The TRW scientists have achieved this by introducing methyl viologen, a chemical which can act as an electron transfer agent for this system. It acts as an intermediate to transfer electrons from an electrode connected to an external power supply to TPN*, making use of plant enzymes or plant catalysts. It has been demonstrated that using this reagent in a chemical solution containing extract of spinach chloroplast, TPN* can be reduced electrochemically to TPNH. The electrochemical process takes place if electrodes placed in the chemical solution are connected to a power supply adjusted to an appropriate voltage. By monitoring the incorporation of carbon dioxide into plant matter, the plant extract produced amino acids and sugar in the same way as by biosynthesis under normal photosynthetic conditions. The production of food by green plants involves the production of ATP also. The possibility of producing ATP within the electrochemical cell is under investigation [*Sci. J.*, **4** (11) (1968), 19].

Get-together on scientific instrumentation

A get-together on instrumentation was organized at the Central Instruments & Services Laboratory of the Indian Institute of Science during 22-23 February 1968. The objectives of the get-together were: (i) to enable the participants to get acquainted with the types of instrumentation problems they face and the progress achieved so far in the development of precision instruments; (ii) to provide a forum for holding discussions among scientific personnel directly involved in similar areas of work and hence establish cooperation between them; (iii) to assess the means available for further work, particularly for the manufacture of laboratory, industrial and research instruments; and (iv) to exhibit various instruments that have been developed by the different organizations.

An exhibition of more than 200 precision instruments, developed indigenously by the Indian Institute of Science (IISc) and by other participating organizations was arranged.

Dr S. Dhawan, Director, IISc, in his inaugural address, spoke about the importance of machines in the modern industrial society and the problems of scientific instrumentation faced by the country due to import restrictions and the growing needs of industry. Reviewing the instrumentation industry in India, he gave comparative statistics for India, UK, USA and Japan. He felt that a concerted effort can bring spectacular results in the field of development of instruments in India and that the government must assist the industry in this process. He explained how the various departments of IISc are designing and developing instruments indigenously for their own use. Dr M. Ramakrishna Rao of the Central Instruments & Services Laboratory traced the activities of the laboratory and gave details of the several instruments developed therein and also mentioned that one and a half lakhs rupees worth of imported equipment were repaired and set right.

Prof N. R. Kuloor (IISc), speaking on the instruments used in the chemical industry, said that automation has come to stay. He explained how the sugar, paper and the textile industries and the petroleum refineries need automation. Prof T. Seshagiri Rao (University of Agricultural Sciences) gave a talk on the problems of instrumentation in the various colleges of the University of Agricultural Sciences. He particularly dealt with the instruments used in soil testing. Shri N. M. Anil Kumar (IISc) gave a technical lecture on 'Development of static relays and their testing'. Wing Commander P. Albuquerque (Hindustan Aeronautics Ltd) spoke on 'The trends in aircraft instrumentation'. Shri B. S. Venugopalan (Bharat Electronics Ltd) spoke on 'Microwave instrumentation in BEL' and Shri S. P. Basheer (Bharat Electronics Ltd) delivered a talk on 'Instruments for radio communication'.

On the second day of the get-together, Shri H. S. Visveswaraiah (Radio & Electricals Manufacturing Co. Ltd) spoke on the 'Manufacture of electric meters in India' in which he described the accuracy and range of induction of water meters and gave statistics about the manufacture of electric meters in India, suggesting guidelines for the future manufacture of electric meters in the country for the internal market as well as for foreign markets in the East except Japan. Shri R. Narasimha Murthy (IISc), speaking on 'Optical instrumentation', traced the history of the optical instruments industry in India and explained its present status. He also described the optical instruments and the components fabricated in the Central Instruments & Services Laboratory of IISc. Dr V. Parameswara (Bangalore Medical College) next delivered a talk on 'Instrumentation for cardiac emergencies'. Explaining the electrical gradient in the heart tissues, he described the electronic instruments developed by him with the assistance of Shri T. G. Krishna Murthy (St John's Medical College, Bangalore) for use in cardiac emergencies to assist the pacemaker of the heart. Shri S. V. Narasaiah (Industrial Estate Manufacturers' Association) spoke on the 'Instrumentation problems in small-scale industries'. Dr R. C. Gupta (Thumba Rocket Launching Station) delivered a talk on the rocket development programme at Thumba and the development and testing of the instruments connected with it. Major M. S. Nagarajan (Chief Inspectorate of Electronics) spoke on 'Electronic instrumentation, their development, evaluation and testing'. He stated that the Bhabha Committee had estimated a requirement of Rs 35 crores of electronic instruments for the ten-year period, 1965-75. The defence was perhaps the biggest single user of electronic equipment, he said, and gave an account of the specifications and standards necessary for the manufacture of these instruments. Shri T. R. Mehta (Chief Inspectorate of Electronics) spoke on the 'Evaluation of errors in measurements, with special emphasis on VTVM'. Shri A. N. Karve and Shri R. S. Yadav (Chief Inspectorate of Electronics) spoke on 'Some aspects of oscilloscope measurements' and 'Measurement of spurious radiation in SSGs' respectively.

At the end of the concluding session, Dr S. Dhawan (Director, IISc) mooted the suggestion that a Society or an Association be formed to organize active work in this field. A committee of members, representing both the industry and the scientific research institutions in Bangalore, was formed with Dr M. Ramakrishna Rao as convener. The function of the group would be to explore avenues for promotion of instrumentation activities in Bangalore by close cooperation among the members on both individual and organizational basis.

M. RAMAKRISHNA RAO

Central Building Research Institute, Roorkee

The annual report of the Institute for 1967 highlights the main achievements and research activities in its major field of work, viz building materials, soil engineering and efficiency of buildings. During the year, emphasis was laid on projects of immediate use to the building industry. Apart from the technical aid rendered to industry in the form of sponsored investigations and consultancy services about 900 technical enquiries were answered. A revised edition of the publication *Climatological and solar data for India* was published.

Studies on red soils, black cotton soils from various places were carried out with a view to assessing their suitability for the manufacture of bricks. Investigations were carried out on the thermal behaviour of brick kilns to achieve a higher yield of well burnt bricks. A process for making magnesium oxychloride terrazo flooring tiles of good dimensional stability was developed. The method eliminates numerous moulds required in the non-pressure method, and saves curing space.

Anticorrosive paints developed at the Institute were exposed at six different sites with different climatic characteristics. An important conclusion from the work on differential thermal analysis of synthetic slag glasses containing

increasing amount of oxides of aluminium and magnesium is that only $CaO\text{-}SiO_2$ ratio should be considered for judging the potential hydraulicity of Indian slags instead of the usual hydraulic indices given in the literature.

A study of the load settlement behaviour of pile foundations in sandy soils showed that considerable economy can be effected by using multiunderreamed piles relative to large uniform diameter piles. A simple technique was developed for the construction of inclined piles required for use in foundations subjected to large lateral thrust. Load tests on concrete footings indicated that boulder material should make a good foundation when the expected load is high.

A protractor was developed for evaluating the sky component for the prevailing Indian sky conditions. By suitably placing it on the plan of the building, the sky component can be read off directly for a given window size. Tables of sky illumination distribution for different room ratios in terms of window sizes were also compiled. An analogue computer built mostly around electrical resistance was set up to simulate all the six surfaces of a room reflecting different quantities of daylight. Analogue studies on the thermal efficiency of perforated bricks showed that bricks with 11-25% perforations are superior to solid bricks.

Thermal conductivity tests on coconut pith-cement concrete of densities ranging from 400 to 800 kg/cu m showed that the best thermal performance was obtained at a density of about 500 kg/cu m. Investigations on the thermal efficiency of hollow, perforated, cavity and light-weight components developed at the Institute were carried out in full size test houses exposed to outdoor climate. Perforated bricks and cored roofing units gave the best performance.

An improved type of corrugated plate solar water heater was designed and fabricated. The usual solar water heater units being rather bulky occupy large volume and entail considerable installation effort. To overcome these, a package type portable solar water heater with a capacity of 90 litres was designed.

Several alternate designs of structures for storage of foodgrains have been developed and their efficiency is being investigated in collaboration with the Central Food Technological Research Institute, Mysore. Studies on optimum utilization of space in hospitals, primary schools, hostels and other buildings have resulted in designs which make for economy in space and user effort.

Announcements

▪ *The Fourth International Congress on Metallic Corrosion* will be held at the International Congress Centre RAI, Europaplein 12, Amsterdam, the Netherlands, during 7-14 September 1969. The congress will be organized by the Nederlands Corrosie Centrum in cooperation with the other Dutch member societies of the European Federation of Corrosion, viz the Koninjlijke Instituut van Ingenieurs, the 'Koninklijke Nederlandse Chemische Vereniging' and 'Bond voor Materialenkennis'.

The congress will deal with two main themes: (1) Corrosion processes; and (2) Protection against corrosion. The following aspects of these subjects will be discussed: fundamental theory and research; experimental methods; and case histories and their diagnosis. Separate technical sessions will be devoted to the following aspects of corrosion processes: (i) Mechanical influences on corrosion; (ii) Influence of radiation on corrosion; (iii) High temperature oxidation; and (iv) Atmospheric corrosion. Six technical sessions will be devoted to the following aspects of the theme 'Protection against corrosion': (i) Inhibitors; (ii) Passivation and anodic protection; (iii) Cathodic protection; (iv) Non-metallic coatings—organic; (v) Non-metallic coatings—inorganic; and (vi) Metallic coatings.

Further details can be had from the Secretariat, Fourth International Congress on Metallic Corrosion, Post Box 7205, Amsterdam, the Netherlands.

▪ *The Ninth International Mineral Processing Congress* will be held at Prague (Czechoslovakia) during 1-6 June 1970. During the congress, the latest developments in the processing of mineral raw materials, including comminution, gravity separation, flotation, magnetic separation, hydrometallurgy and other chemical treatment techniques, thermal treatment, automatization of mineral processing and waste water treatment will be discussed. As a part of the main session of the congress a symposium on agglomeration (pelletization, sintering, new methods of agglomeration and utilization of prereduced pellets) will be held. A large number of papers by specialists from various countries including India will be presented at the congress. The official congress languages will be English, French, German and Russian.

Further details regarding the congress can be had from Shri P. I. A. Narayanan, Officer-in-Charge (Ore Dressing), National Metallurgical Laboratory, Jamshedpur 7, who is the Member Correspondent from India of the International Scientific Committee of the congress.

▪ *The Third International Conference on Congenital Malformations*, sponsored by the American voluntary health agency, "The National Foundation — March of Dimes", and being organized by the International Medical Congress Ltd, New York, will be held at the Netherlands Congress Centre, the Hague, the Netherlands, during 8-15 September 1969. Further details regarding the conference can be had from the Conference Secretariat, c/o Holland Organizing Centre, 16 Lange Voorhout, the Hague, the Netherlands.

▪ *The Seventh International Congress of Diabetes* will be held at Buenos Aires, Argentina, during 23-28 August 1970. Details regarding the congress can be had from Dr Virgilio G. Foglia, President, or Dr R. A. Chieri, Secretary, Seventh Congress, International Diabetes Federation, Paraguay 2155, Seventh Floor, Buenos Aires, Argentina.

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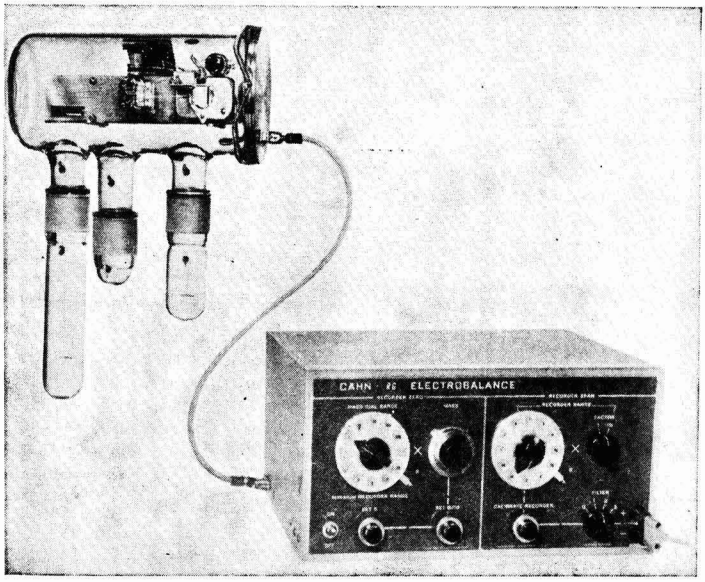

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