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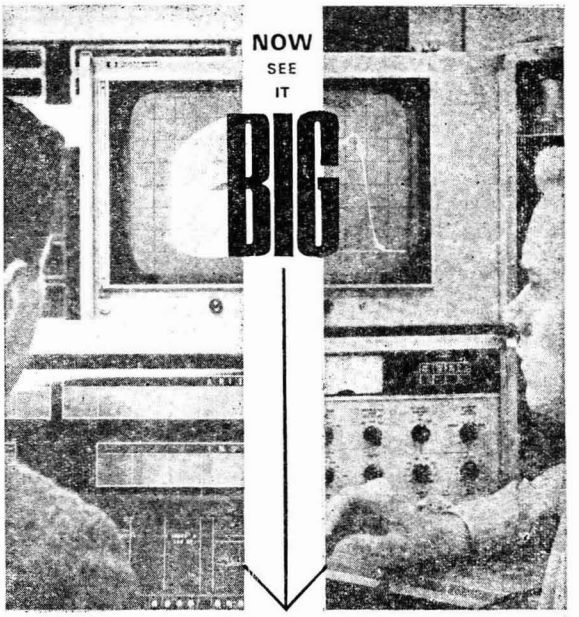

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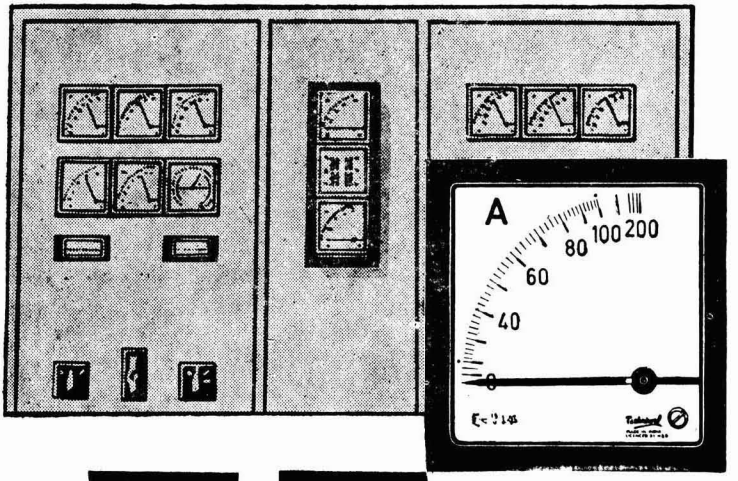

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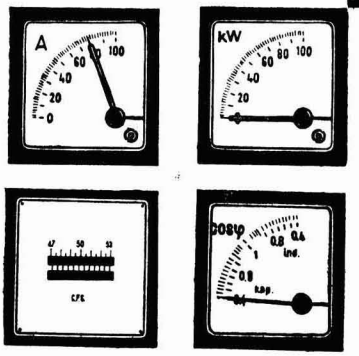

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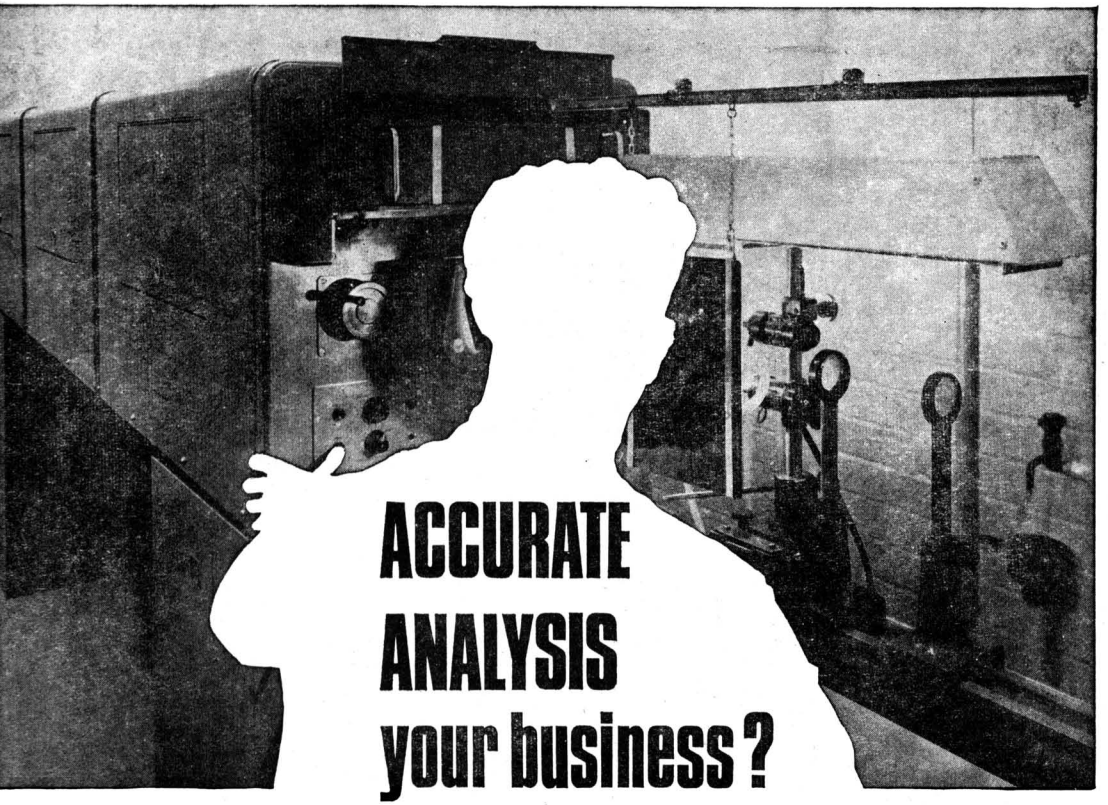

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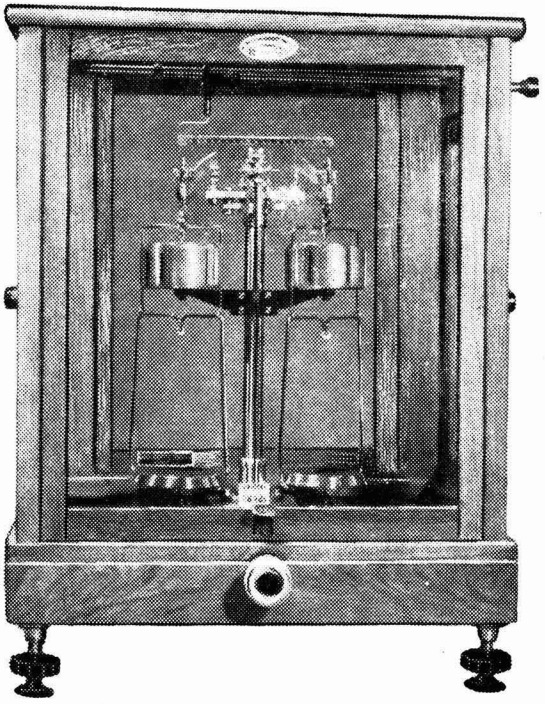

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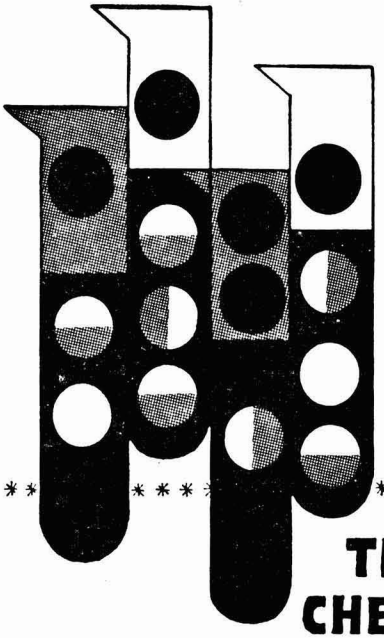

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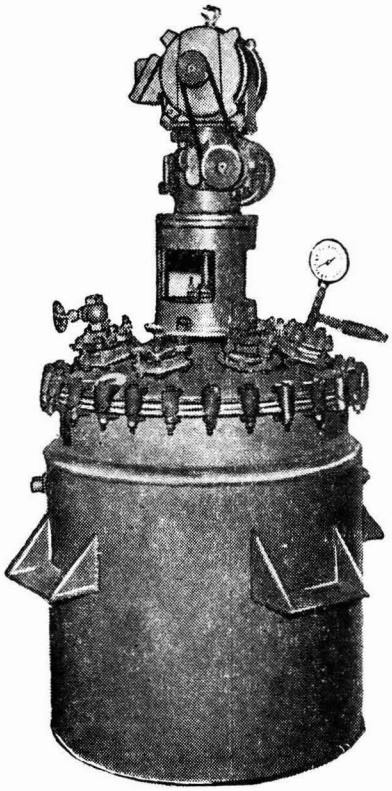

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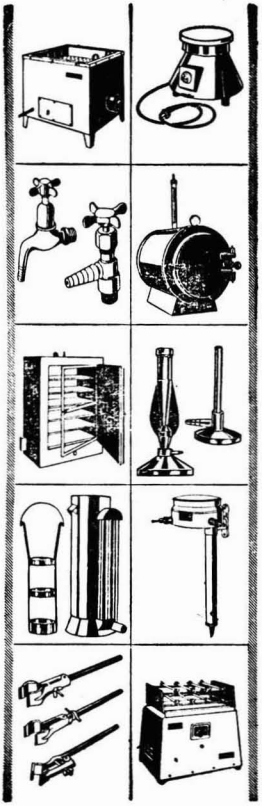

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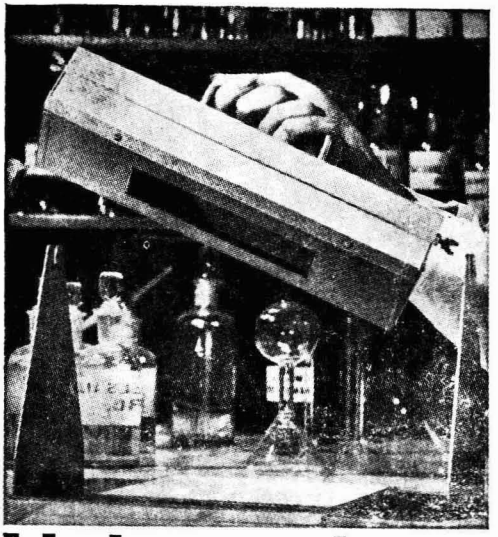

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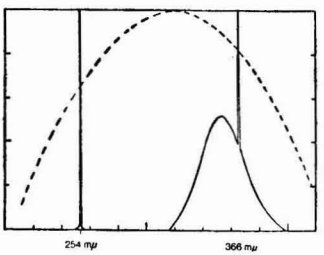

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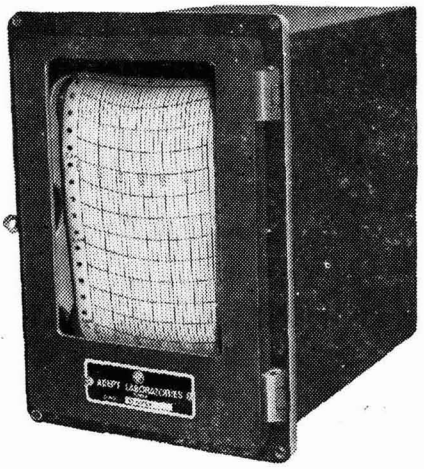

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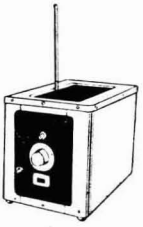
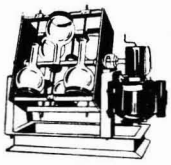


SEROLOGICAL BATH

ELECTRIC OVEN

PARAFFIN EMBEDDING BATH

SHAKING MACHINES



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Current Topics

International Facility for Space Research

THE dedication of the Thumba Equatorial Rocket Launching Station (TERLS) to the United Nations on 2 February by the Prime Minister, Shrimati Indira Gandhi, and the inauguration of the Indian Rocket Society the following day mark the beginning of a new era of international cooperation in the field of space research. TERLS owes its establishment to India's ready response to a UN offer made to its member nations in 1962 to accord its sponsorship to an equatorial launching base to be established as an international facility for peaceful uses of outer space and for scientific investigation of the upper atmosphere. Being the only land-based rocket launching station in the world situated near the geomagnetic equator, TERLS fills one of the major gaps in the global coverage of the upper atmosphere by sounding rockets. The Station is ideally situated for studying the geophysical phenomenon of equatorial electrojet, unique to the equatorial atmospheric profile. This phenomenon, not yet fully understood, is known to have a profound influence on the make-up of the global weather. TERLS also offers a rare facility for research on the winds of the mesosphere (30-60 km.) and in X-ray astronomy.

Thanks to the generous contribution and unique cooperation of many countries to this project, TERLS has already become a well-equipped space research centre with all the facilities needed to launch a variety of sounding rockets. The equipment provided by USA includes two rocket launchers and a telemetry receiving station and that by USSR, an MI-4 helicopter, for range surveillance and payload recovery duties, a transistorized electronic computer and equipment for payload testing. France has gifted a launcher, a radar and a high-speed camera for photographing of rockets. The rest of the essential equipment was fabricated and supplied by the Department of Atomic Energy. The facilities available at the Station include vehicle assembly, payload preparation and check-out, block-house for the launching crew and project scientists monitoring the payloads until the time of firing, telemetry, tracking radar, meteorological support and computation for programming and data analysis. The Station has a creditable record of experimentation, with 56 successful launchings — 29 Judi-Dart meteorological rockets, measuring winds in outer space between 30 and 70 km.; 20 Nike-Apache rockets utilized for measuring atmospheric winds, temperature, diffusion and turbulence by photographing the trail of the ejected sodium vapour from special camera stations; and 7 Centaure rockets for investigating the atmosphere extending up to 160 km. A matter of even greater satisfaction is the successful launching of three 'Rohini' rockets developed entirely indigenously. In addition to making scientific observations connected with the rocket launching experiments, the Station has made considerable headway in designing and developing various sophisticated items of electronic and mechanical hardware and other special devices. These include telemetry transmitter, electronic timers, antenna systems and other ground support equipment. Through indigenous effort 8 different types of rocket nose cones, payload housing and canisters, mechanical timers and nose cone ejection systems have been developed. Another notable achievement is a Dart payload system for meteorological rockets which after severe flight tests has already become operational.

Under the direction of the Indian National Committee for Space Research (INCOSPAR), TERLS has an ambitious programme of activities for the immediate future, including radio frequency mass spectrometer experiments in collaboration with the Max-Planck Institute of West Germany, rocket launching experiments for investigating X-ray sources in space, intensive radio propagation studies and manufacture of Centaure rockets in collaboration with Sud-Aviation of France.

The main objectives of the Indian Rocket Society, with its headquarters located at TERLS, and inaugurated on 3 February by Dr Luigi G. Napolitano, President of the International Astronautical Federation, Paris, are: (i) to promote and stimulate space flight activities to achieve scientific knowledge of outer space for peaceful purposes; (ii) to secure widespread dissemination of technical and other information on space flight through exchange of ideas, publications, research collaboration, etc., between members; (iii) to stimulate public interest in and support for the idea of space flight; and (iv) to stimulate work on astronautical subjects by the national establishments engaged on space research, scientific institutions, universities, commercial and industrial firms, individual specialists, etc.

The two events, viz. the dedication of TERLS to UN and the establishment of the Indian Rocket Society, are bound to provide considerable fillip to their respective avowed objectives — international collaboration in respect of scientific investigations directed towards peaceful uses of outer space, and promotion of national effort in the field of space research. An important contribution of TERLS in promoting international collaboration will be the provision of facilities for space research to such member states of UN as are unable, because of economic or technological factors or the unsuitability of their territories to support sounding rocket programmes except through cooperative effort.

Methods of Measuring Vapour Pressure of Water & Other Liquids

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ACCURATE determination and control of vapour pressure of liquids, specially water, have important implications in sorption studies, air-conditioning, manufacture of many equipment, components, etc. Different methods are required to determine vapour pressure or relative humidity, depending on the nature of the problem. A chronological and comprehensive review on hygrometry has been published by Gregory and Rourke[1]. Nesmeyanov[2] has also reviewed the methods of vapour pressure measurement. The present review is an attempt to make the information on methods for the measurement of vapour pressure up to date.

General Methods

Earlier methods of measurement of water vapour in atmosphere were based on the determination of increase in weight of adsorbents, such as wool, silk, cotton, etc. Latham and Stow[3] determined the relative humidity of air from the magnitude of the vertical movement accompanying the mass changes in a ventilated ice sphere suspended by means of a quartz spring. The changes are indicated by an optical device. Relative humidity can be determined within an accuracy of 5 per cent over the temperature range 0-60°C. This method is useful in industrial practice. Due to moisture adsorption, the dimensions of some materials increase. Rocha[4] used the expansion of timber caused by the adsorption of water vapour to measure the relative humidity in cavities of dams. He measured the change in dimension from the strain caused on a thin vibrating wire. The change in vibration due to the strain was calibrated to read the relative humidity. Hair is another material commonly used to determine relative humidity. Muller[5] has termed such materials used for determining relative humidity as humidity sensors. Iles and Worsnop[6] discussed the working of a single hair hygrometer under varying conditions of temperature and humidity. Davey[7] has discussed the sensitivity of hair hygrometers. Lebedeff[8] used this type of hygrometer to measure relative humidity of soil air. Gregory and Rourke[1] found that impregnated fibre glass yarn suspended from the arm of a sensitive balance, calibrated over sulphuric acid of different strengths, forms a highly sensitive hygrometer for use in both industrial and research practice. It has the additional advantage that the effect of temperature variation is almost negligible.

Any non-volatile liquid (generally mineral oils) can be used in a U-tube manometer to measure pressure difference. For greater pressure difference mercury manometer is used. A mercury U-tube manometer is simple to construct, requires no calibration and operates over a wide pressure range[9]. With each arm connected to a separate region, the manometer can be used to obtain differential pressures or can be used as a null device. Commonly, one arm is evacuated and the manometer indicates the total pressure directly. The closed type manometer (containing some air) works on the principle of Boyle's law. McLeod gauge[10] works on this principle and can be used to measure pressures as low as 10^{-6} cm. Hg. It is important that the gas whose pressure is being measured should not condense under pressure used to measure the volume in the capillary tube of the manometer. In a capillary method for determining saturation vapour pressures of liquids reported by Borrell and Nyburg[11], saturated vapour mixed with air is trapped in a capillary by means of a free moving mercury pellet. At low temperatures, vapour pressure becomes negligible and the trapped volume contains only air. Thus vapour pressure at high temperature can be calculated. Douslin and Osborn[12] designed an inclined piston gauge which can be used in thermochemical research for accurate determination of vapour pressures in the low and intermediate ranges. Accuracy of the gauge proper lies in the range 0·001-0·012 Torr. According to Nesmeyanov[2], a cover of non-volatile liquid should be used when the pressure of a vapour capable of reacting with mercury is to be measured. Inclined manometers have higher sensitivity. Inclined manometers containing glycol were used by Quitzsch to measure vapour pressure very accurately[2]. Bourdon gauge[13], which consists of a spiral metal tube of oblong cross-section with one end open and exposed to pressure, can measure high pressures of the order of a few atmospheres. The pressure causes the tube to straighten and this is conveyed to a pointer. Barrer and Wasilewskai[14] measured vapour pressure down to a very low value (0·05 mm. Hg) with a spiral gauge consisting of a hollow spiral connected to a vapour chamber; the spiral itself is enclosed in a separate chamber in which any desired pressure can be created. The change in pressure is measured by the deflection of a mirror attached to the spiral. It can measure pressures in the range 1-760 mm. Hg and up to 350°C. Foord[15] made a Bourdon type manometer combining both spiral and membrane principles which can measure pressures from 1 mm. to 1 atm. and can also be used at high temperatures. Nesmeyanov[2] constructed a manometer containing a thin flexible membrane (on which a small mirror is attached) sealed into an expanded glass tube attached to a vacuum system. The pressure change causes flexing of the membrane, which is observed by lamp and scale arrangement. A pressure difference of 10 mm. Hg can be measured by this device with an accuracy of 0·01 mm. Hg. This manometer is specially useful for measuring pressure of gases corrosive to mercury. Aneroid manometer[16] is a partially exhausted cylindrical metal box with top slightly deformed by change of pressure. This deformation can be magnified by a set of levers and

can be used to measure pressures around atmospheric pressures. Grotyohann[17] constructed a pressure gauge, which nulls automatically pressure differences across a spoon gauge by optically coupling a servo control. Pressure up to 1 atm. can be measured with an accuracy of 0·5 mm. Hg. This apparatus is specially useful for measuring the vapour pressure of sulphur trioxide.

Knudsen[18] absolute manometer can be used to measure low vapour pressures. In a rarefied gas, if two plates are at different temperatures and are at a distance less than the mean free path of the gas molecules, then the force with which the gas molecules act on the cooler plate is not the same on both the sides. The difference of the above force is proportional to pressure. To determine gas pressure, the repulsive force between the two plates is measured.

Psychrometers

According to Middleton and Spilhaus[19], of all the ventilated psychrometers, the simplest and the cheapest is the sling psychrometer or whirling psychrometer and Assmann psychrometer is one of the best ventilated psychrometers. The smaller the bulb of the thermometer, the less the wind speed necessary to obtain the maximum depression in temperature[19]. Thus a thermocouple wound with very fine cotton fibres could be used as a wet bulb thermometer. Simons[20] using copper-eurek thermocouple determined relative humidity between 0 and 10 per cent and down to −40°C. Powell[21] fabricated an apparatus incorporating a 40 SWG nichrome-constantan thermocouple. Richardson[22] used a thermocouple type recording psychrometer for measuring relative humidity in hot and arid atmospheres. The technique utilizes dry and wet thermocouple sensors with each output recorded on a potentiometer recorder. To eliminate error due to heat conduction, the wet bulb contains precooled water. Box[23] designed a thermocouple psychrometer which uses Peltier cooling to condense water on to the wet bulb thermocouple junction to measure the relative humidity in the range 98·4-100 per cent. Richards[24] also designed a thermocouple psychrometer for measuring the relative vapour pressure of water in liquids or porous materials, having a sensitivity of 0·002 per cent relative humidity at high humidities. Shiba and Tozawa[25] fabricated a wet and dry plate dew point hygrometer. A graph between dry bulb temperature and temperature difference (between dry and wet bulbs) is plotted and the dew point temperature is determined by extrapolating the line to read zero difference in temperature. Worrall[26] described a psychrometer for determining vapour pressure of water in air with dry bulb temperature exceeding 100°C. This can be done provided the wet bulb temperature does not exceed 100°C. and with some other limiting conditions. Branton[27] reported a method to measure relative humidity with a psychrometer at temperatures below freezing point. Collins[28] made a platinum resistance psychrometer with a moistened cotton sheath and used it as a wet bulb thermometer. Taylor[29] discussed the response of such psychrometers to fluctuations in relation to vapour pressure.

Dew Point Hygrometers

Dew point methods, according to Bemis[30], are at present the best for the determination of relative humidity as far as accuracy at low humidities is concerned. Paine and Farrah[31], after reviewing the literature on measurement of vapour pressure, selected the dew point apparatus for meeting the performance objectives. Dew point measurements can be used for vapour pressure determinations over very wide ranges of moisture contents. Frost point hygrometer, a modification of the dew point hygrometer, is reported to be useful for detecting the humidity of extremely dry gases[1]. Dobson and Brewer[32] found that dew point methods are satisfactory even at low temperatures and all that is required is to note the temperature of the surface when a thin deposit of dew is neither increasing nor decreasing. According to Paine and Farrah[31], dew point is the temperature at which a deposit of dew or frost on a non-sorptive inactive surface is maintained without transfer of vapour to and from the surface. According to Regnault's principle, dew point of air is the temperature at which air must be cooled at constant pressure and constant water vapour content to become saturated. On the other hand, according to Gregory and Rourke[1], adsorbed water exists on glazed surfaces at temperatures higher than the dew point. The surface films are so thin that at that stage all liquid molecules are in the range of attraction of atoms of the solid surface. When temperature is lowered, the thickness of the adsorbed layer increases beyond the influence of atoms of the solid surface and only then the surface tension forces become important and fine drops are formed. Thus the dew point may be considered as a sequence of phases throughout which the moisture phase changes from an adsorbed film to the liquid phase. The range of temperature throughout this droplet phase is probably of the order of a fraction of 1°C. This phase may be regarded as representing a stable state of equilibrium and over this narrow range of temperature, the transfer of vapour to or from the cooled surface is zero. Most dew point instruments, including that of Regnault, do not operate strictly according to Regnault's principle. They create a temperature gradient between moist gas and the cold surface and the correction due to this is serious under dry conditions.

According to Hartley *et al.*[33], the major requirements for dew point measurements are: (i) a relatively clean polished surface for dew collection, (ii) a means for detection of dew or frost, and (iii) an accurate and stable method to measure the surface temperature. Paine and Farrah[31] also discussed these requirements, including a compensated controlled amplifier. Cooling and heating arrangements and ventilation are among the other requirements.

It is not usually possible to measure the surface temperature of a body accurately and it is difficult to judge the beginning of condensation[19]. According to Wylie *et al.*[34], the temperature at which condensation begins abruptly represents only an approximation. While determining the frost point between zero and −20°C., dew comes as a nuisance on fresh

surfaces and it could be overcome by cleaning the surface by saliva[35]. Wylie *et al.*[34] discussed two probable causes for error in the determination of dew point temperature. A perfectly clean surface for dew collection is not achievable, since there is water-soluble matter which causes incipient condensation at temperatures well above the true dew point. This lowers the vapour pressure due to Raoult's effect. The fine drops also cause elevation of vapour pressure due to Kelvin effect. This effect can act as a barrier to droplet growth. The effect is also important in the growth of deposits in which coalescence is occurring. Kelvin effect is encountered if an accuracy better than 0·2°C. is sought. John and Sekhon[36] found that deposits of vapours of liquids like carbon tetrachloride and ethyl formate on the surface take the form of thin films; some colour patterns are obtained at the dew point, indicating that the film thickness is of the order of a few molecules. Water vapour takes the form of fine drops. It follows that since the surface is not wettable by water and since water has high surface tension, fine drops are formed. Since the surface is wettable by liquids like carbon tetrachloride and ethyl formate and since they have low surface tension, films are formed.

With some skill, visual observation can give satisfactory results[37]. Observation of dew formation can be facilitated by making a mark on the thimble with a very thin smear of grease. Dew can, however, be more easily detected on a flat surface. To facilitate the detection of dew, air may be blown across the disc as a narrow jet. The surface must be cooled slowly. Only one-half of the disc is cooled, so that a contrast is obtained between the dewed and dry metal. John and Sekhon[36,38] used a concentric nickel-plated copper ring around the cooled surface to distinguish the dewed surface. Wylie *et al.*[34] found that the dew deposit is barely visible optically when the deposit is 3 μg. per sq. cm. and photoelectrically at 1 per cent of the above value. According to Brewer[35], frost or dew formation at the frost or dew point should be viewed with oblique, background illumination with a low power optical magnification. Thornthwaite and Owen[39] detected dew formation by a photocell and Armstrong[40] used a photodiode for the purpose. Ballinger[41] detected frost deposit by the energy attenuation of alpha radiation. Martin[42] used a barrier layer photocell connected to a galvanometer to detect dew formation. Kobayashi[43] detected and measured dew point on the basis of a sharp increase in the ionization current (produced by alpha rays) when dew formed on the surface.

Surfaces which are poor conductors of heat are not good dew collectors. Dew collecting surfaces should have negligible temperature gradient radially across the surface and axially through the region of temperature sensor to achieve maximum accuracy[31]. Silver, copper, etc., have good thermal conductivity and minimum temperature gradient and hence they are ideal for dew collection. For fast response, the mirror size must be as small as possible. It should retain sufficient area and volume to avoid complication in photodetector alignment and temperature sensor mounting. A 0·06 in. diam. mirror has been found to be a good compromise[31]. The small mirror also permits operation at very low sample flow velocities without increasing the response time. By using a small mirror very small volume of the sample suffices. Rhodium plating gives best performance because of its high reflectivity and excellent resistance to corrosion. According to Martin[42], for the temperature of the mirror to respond rapidly to changes in heater current, it is necessary that thermal diffusivity be high. Silver being rather soft, a silver mirror is easily damaged by repeated cleaning. An alloy of 80 per cent silver and 20 per cent copper is much more satisfactory. Brewer[35] used black anodized aluminium with a perfect upper surface. Hartley *et al.*[33] used a polished stainless steel disc as a mirror. The surface on which dew is deposited should be of metal either brightly polished (silver, stainless steel, etc.) or with glossy black finish (anodized or stoved enamel)[37]. John and Badgley[44] and John[45] fixed a thermocouple in a hole a few mm. below the end of a copper rod. Then a plastic concentric cylinder of a few cm. length was cast at that end around the copper rod. The end was faced until the thermocouple was just beneath the faced surface. The surface was nickel-plated. The concentric plastic cylinder kept the nickel-plated surface at a uniform temperature. According to Brewer[35] and Hartley *et al.*[33], a thermocouple just beneath the surface is probably ideal. According to Hartley *et al.*[33], a thermocouple fixed at the surface (not beneath) will keep the contact points at higher temperature, compared to other parts of the surface, due to heat flow through the thermocouple. They measured dew point over the range −30° to +30°C. with an accuracy of ±0·002°C. around 0°C. Brewer[35] observed that copper-constantan thermocouple gives high accuracy, long-term stability and conformance with standard calibration curve. He measured dew point down to −90°C. Martin[42] used a platinum resistance thermometer consisting of nine turns of 0·0008 in. diam. wire wound into a thread. Since the winding is round the skirt of the thimble, it does not acquire the temperature of the mirror surface. But it can be calibrated to read the surface temperature with a thermocouple. The output of the resistance thermometer is measured by a Wheatstone bridge. He measured the frost point down to −80°C. In another apparatus, Martin[46] used a pallador thermocouple welded to the surface of the mirror. Paine and Farrah[31] measured dew point by a copper-constantan thermocouple using 0·005 in. diam. wire within the range +50° to −65°C., with an accuracy of ±0·01°C. over the entire temperature range. Nathan[47] used a thermistor as a dew or frost point sensor over the range 0° to −43°C. and obtained values with an accuracy of ±0·7°C. Francisco and Beaubien[48] used a platinum resistance thermometer element physically integrated with the mirror structure to provide linear temperature read out. They measured temperatures from −20° to +70°F. with an accuracy of ±0·5°F. According to Dobson and Brewer[32], even at −80°C. it is not difficult to detect the deposit changes of the order of 10^{-8} g. of ice

corresponding to a uniform thickness of 1 atomic diam. on the thimble. This is possible because ice is deposited as large number of small crystals which scatter light very efficiently. A fundamental characteristic of the apparatus is that dew point is independent of deposit thickness within a limited thickness range.

Ventilation is very important in dew point measurements. Brewer[35] observed that dew or frost point measurement is made more sensitive if the surface is properly ventilated. The ventilation produced by 2-10 cm. of water pressure through an adequate jet is usually sufficient. But the surface should not be exposed directly to air moving at speeds above 2-3 ft per sec.[37]. John and Sekhon[36] and John[45] also used ventilation for determining dew point by means of a small fan run magnetically.

Cooling of surface to measure dew point is best achieved by Peltier cooling[40]. Peltier coolers capable of attaining temperature up to −100°C. have been designed. Griffin and Stringfield[49] cooled the mirror by thermoelectric cooling. Cambridge Systems Inc.[50] used Peltier cooling to cool rhodium-plated mirror. Brendeng[51] used cold alcohol to cool the mirror by cooling the underside of the mirror. Martin[42] cooled the underside of frost collecting surface by means of a jet of nitrogen. Fraser and Weart[52] described an apparatus for measuring dew point between −190° and −80°C. using evaporating liquid nitrogen as coolant. Dobson *et al.*[53] used solid carbon dioxide and petrol as coolant.

Automation has been increasingly adopted in hygrometry. According to Brewer[35], one method of operation involves the continuous cooling of the deposition surface. In the absence of a deposit the temperature of the surface lowers until a dew or frost deposit is formed. This is detected photoelectrically by means of a suitable servo amplifier. Then the servo-mechanism supplies heat to the surface to control the deposit on the mirror at a constant level. Alternatively, if no dew is present on the mirror the servo-mechanism may produce cooling in the Peltier element. This cooling is switched off or controlled when the deposit reaches the required value. In this case Peltier cooling balances natural heating. Thus the surface can be held at the dew point. Most mechanical servos are inherently oscillatory. In mechanical servo, stability is provided either by friction or by phase advance networks. Thornthwaite and Owen[39] designed one of the first automatic dew point apparatuses in which the cooling surface is the end of a copper rod immersed partially in a freezing solution in a Dewar flask. As soon as dew is formed on the surface it is detected by a photocell and a small heating element placed just beneath the polished surface is switched on; when the dew disappears, the photocell switches off the heater. The thermocouple attached to the plate measures the temperature or it can be arranged for recording the output. A fundamentally similar apparatus designed by Burton Manufacturing Co.[54] consists of a polished mirror and an associated electronic servo loop to maintain the mirror at dew point. Cambridge Systems Inc.[50] used scattering type optical system to sense the dew and control the temperature of the mirror. Armstrong[40] detected dew formation by means of a photodiode. When condensation takes place, the light is diffused and less light impinges on the diode. The amplifier, operating as a proportional control, reduces the current to the thermoelement of the cooler and hence the surface temperature tends to rise. The condensate disappears, impinging more light on the diode. Thus the dew point can be determined keeping the temperature constant. Ballinger[41] detected frost deposit by the energy attenuation of alpha radiation. An automatic control maintains a constant mass deposit of frost on the cooler surface by means of a thermoelectric cooler. Energy attenuation of alpha particles is same if equal mass deposits of water or any of the crystalline form of ice and the sensitivity remains constant irrespective of the state of water. The instrument responds to a 1 μg./sq. cm. change in frost layer thickness. Nathan[47] used photoelectric balancing to control r.f. induction heating of the mirror and dry ice cooling to maintain frost point. The deposit of dew was observed by Brendeng[51] by a photoresistor connected in a bridge, the output from which is fed to a servo amplifier with a servo-motor and a motor-operated air pressure valve. The air pressure is recorded by means of a strain gauge pressure transducer and stripchart recorder. Francisco and Beaubien[48] designed an automatic dew point hygrometer based on thermoelectric cooling.

Radiation Manometers

Radiation manometers (a misnomer) work on the principle that radiation is reduced to the minimum in comparison to the conduction of heat. Conduction depends on mean free path, which in turn is inversely proportional to vapour pressure. When the distance between the hot and cold surfaces is less than the mean free path of the molecules the loss of energy due to heat conductivity at low pressure depends linearly on the gas pressure. When the heat supplied to the heated wire is kept constant, the temperature of the wire will change with pressure of the surrounding gas. The temperature of the wire is measured by a thermocouple, resistance thermometer, or from the expansion of the wire. Barrows and Howard[55] measured the temperature and vapour pressure in diffusion cloud chambers by means of a platinum resistance wire in which current was varied. This enabled the calculation of supersaturation in the chamber. In the Pirani manometer[56], current is kept constant and the change in resistance is measured. The wire is heated to any temperature in the range 100-200°C. and a milliammeter is placed across the Wheatstone bridge which in turn measures the temperature of the wire. Nesmeyanov[2] described a bimetallic strip through which current is passed. The bimetallic strip terminates in an indicator which moves along a scale. For current of given voltage the deflection of the indicator is a function of gas pressure.

Heat of Adsorption Manometers

Heat of adsorption depends on the relative pressure of the vapour. This being exothermic, at

higher relative pressure, more heat will be evolved by a very dry adsorbent leading to rise in temperature, which can be used as a measure of the relative pressure. Downes and Nordon[57] designed an ultra dry bulb hygrometer using the above principle. Flumerfelt[58] also measured water vapour concentration from heat of adsorption by an adsorbent. Gregory and Rourke[1] described a thermal hygrometer based on the principle that adsorption or desorption of moisture from cotton wool is accompanied by a rise or fall in temperature of the adsorbing material. The change in temperature measured by a thermoelectric circuit is used to determine the environmental humidity.

Viscosity and Diffusion Manometers

Diffusion velocities of different gases through a porous solid are of different magnitude. This principle is made use of in the manometers introduced by Greinacher[58a]. The rate of damping of a vibrating quartz fibre leaf depends on the pressure when it is of the order of 10^{-2} to 10^{-5} mm. Hg. Hence this property is used to measure pressure in this range. Morecroff[59] determined the vapour pressure of high boiling point liquids by measuring the recoil force produced by its vapour effusing through a small hole into a high vacuum. He was able to measure vapour pressures of the range 10^{-5} to 10^{-1} mm. Hg. Silva *et al.*[60] described an inverted capillary technique of measuring normal boiling points which has been modified for measuring saturated vapour pressure up to 135 atm. and up to 1000°C.

Electric Hygrometers

The measurement of the true electrolytic resistance of a hygroscopic solution in an equivalent cell contained between two plain parallel platinum electrodes as a function of relative humidity and temperature forms a system which is a true electrolytic hygrometer. In this, the cell solution is in equilibrium with the external relative humidity. Steps are taken to overcome the effects due to polarization.

Out of a number of hygroscopic salts, lithium chloride is the one most commonly used. According to Smith and Hoeflich[61], lithium chloride element has a number of disadvantages, such as polarization, slow response to humidity changes, large temperature coefficients, film wash out due to heavy fog, etc. Fukuda[62] used this type of hygrometer to measure relative humidity of soil air *in situ*. Dunmore[63] was one of the first to make a lithium chloride hygrometer. He used tin-coated copper as the electrode and later used palladium. Mathews[64] observed that partially hydrolysed polyvinyl acetate could release charged gas bubbles from electrodes due to its detergent activity. He also found that by moving the electrodes apart, the resistance-relative humidity curve was flattened. The slope of the resistance-relative humidity curve varied with the metal used as electrodes. Tin polarized less with lithium chloride solution than many other metals including gold. Mathews[65] found that ventilation, thinning of lithium chloride solution and addition of aluminium chloride improved the performance of the hygrometer. He controlled polarization by using a.c. measuring circuits. According to Kobayashi and Toyama[66], the physical and chemical changes in electrodes and moisture sensitive film are the main cause of the ageing effect. A small amount of gelatine added to lithium chloride-polyvinyl alcohol solution improved the performance of humidity sensing elements. Handegord and Till[67] used Dunmore type hygrometer to measure humidity at low temperature. Rogers[68] made a very small sized Dunmore type hygrometer to measure relative humidity just below the leaf surface with an accuracy of 1 per cent or better. Heated lithium chloride electric hygrometers were used by Hedlin and Trofimenkoff[69]. Szalai[70] designed a lithium chloride impregnated ceramic tube hygrometer with a thin wall to measure relative humidity in the temperature range 0° to −30°C. It can be used to measure the environmental relative humidity of food preserving chambers. Brastad and Borchardt[71] designed a miniature Dunmore type hygrometer fitting inside the end of a hypodermic needle. Relative humidities associated with surfaces as small as 0·001 sq. in. have been measured.

Johnson and Duggan[72] constructed a cerium titanate type humidity transducer. The temperature effect in this apparatus is small and the response of the element shows exponential relationship with relative humidity. Jones[73] tried to measure relative humidity from the change in the resistance of the lead iodide film. He also used a thin film of barium fluoride deposited on a glass substrate as the humidity sensing element. The electrical impedance of the element varies about three orders of magnitude with relative humidity in the range 20-100 per cent. Hysteresis effects are negligible. Musa and Schnable[74] made sensing element by spraying a suspension of crosslinked polystyrene sulphonic acid particles on to a polystyrene cell having two electrodes. Variation in the resistance of the element with relative humidity is the result of change in ionic conductivity of the hydrophylic film with properties similar to those of ion exchange resins. Wylie[75] designed an absolute hygrometer of high accuracy based on measurement of the resistance of an ionic crystal of calcium chloride. The useful range of the hygrometer is continuous down to −55°C. with an accuracy of 0·1 per cent relative humidity. King[76] designed a piezoelectric sorption hygrometer in which the sensing element is a radio frequency quartz crystal coated with a hygroscopic material. In a simple circuit using a crystal of this type the frequency of oscillation falls when the crystal gains weight due to the adsorption of water. The change in frequency, which is a function of relative humidity, can be measured accurately and rapidly.

In another type of electric hygrometer, carbon film elements are used in which the resistance of the element varies with change in the volume of the film and thus indicates humidity changes. The resistance increases with increase in humidity; this is reverse of what happens in the electrolytic film element. The time lag and temperature coefficients for the carbon film element are less than those of an electrolytic film element. The carbon humidity element used by Stine[77] consists of a flat acrylic

strip with long edges coated with a gelatinous cellulose coating containing finely divided carbon particles in suspension. Smith and Hoeflich[61] designed a carbon film electric hygrometer in which, instead of relying upon the change in electronic conductivity through a film of electrolyte, the new element responds to the changing resistance of a thin film of electronically conducting material.

Electrolytic Hygrometers

The electrolysis of adsorbed water in phosphorus pentoxide due to a constant applied voltage makes the electrolytic current of the system exactly proportional to the amount of water adsorbed. This principle is made use of in the construction of electrolytic hygrometers. The choice of electrodes is to be such that the anode does not get dissolved in the electrolyte due to the electroplating effect. The hygrometer unit utilizes a phosphorus pentoxide electrolysing cell in series with a battery which allows the flow of current proportional to the rate of absorption of water vapour. The electrolytic moisture cell differs from the electric hygrometer in that the conducting film is electrolysed continuously by an applied d.c. voltage and the cell current rather than the cell resistance is measured as a function of the moisture content[78]. To get better distribution of moisture over the electrodes at high humidity levels, Czuha[78] isolated the platinum electrode from the atmosphere by a teflon porous hydrophobic diffusion barrier. In these cells, the control of mass rate of water is required and has to be kept in the range 5-10 ml. per minute. Jones and Petersen[79] developed an electrolytic cell using rhodium electrodes instead of platinum with service life 4-6 times longer compared to the cell with platinum electrodes. This is due to low catalytic activity of rhodium compared to that of platinum. The two main defects of a cell with platinum electrodes are the high moisture levels and the hydrogen combination. The first is due to shorting of the electrodes, characterized by the formation of a black deposit between the electrodes. The second is due to the reaction of the electrolytically generated oxygen with hydrogen to form additional water. This reaction is catalysed by the platinum of the electrodes. MacCready and Lake[80] have listed eight main features of such cells. According to them the phosphorus pentoxide moisture sensor is a chemical moisture trap and it maintains a very low water vapour pressure and equilibrates quite rapidly. Their electrolytic cell had two platinum electrodes wound as very tight double helix on the inside of a glass tube. The electrolyte, phosphorus pentoxide, is introduced as a 10 per cent solution in acetone. The cell calibration is 93·5 μg. of water corresponding to 1 coulomb of charge passed through the cell. Crawshaw and Davidson[81] described an electrolytic hygrometer for measuring the moisture content of gases down to a few p.p.m. The hygrometer records the water content of suitable gases continuously.

Gregory and Rourke[1] observed that the electrolytic hygrometer is extremely sensitive to changes in relative humidity. The effect of lag in a properly designed instrument is almost negligible. Morris and Sobel[82] gave a simplified theory on the speed of response of the electrolytic hygrometers. They suggested some methods for obtaining maximum speed of response. Goldsmith and Cox[83] used an improved type of electrolytic hygrometer with electrolytic surface having phosphorous pentoxide-phosphoric acid film. The hygrometer operates over the range 0·5-5000 p.p.m. of water vapour and the response is between 5 and 15 sec. A pressurizable version of Goldsmith-Cox hygrometer has been used to measure water vapour as low as 0·01 p.p.m. by volume at higher working pressures[84].

Capacitance Hygrometers

The capacity of a condenser changes with density of the medium acting as the dielectric. Hence this property is used to measure water vapour pressure in gases used as dielectrics. Underwood and Houslip[85] used a capacitance hygrometer to measure vapour pressure in a small enclosed space. The response of the hygrometer, which is satisfactory, depends upon the frequency of the applied potential difference up to 80 per cent relative humidity. Nelson and Amdur[86] designed a relative humidity sensor based on the capacitance variation of a plastic film condenser. Charlson[87] measured relative humidity by noting the change in dielectric constant of a mixture of a hygroscopic liquid and an inert solid in the path of the gas flow. Utterback and Griffiths[88] designed a reliable submicron pressure reading capacitance manometer. The capacitance manometer consists of a metallic diaphragm separating two chambers, the measurement side and the reference side. A pressure difference between the chambers moves the diaphragm and an electrode on one side, while decreasing the capacitance on the other side. This principle is used to measure pressure of He, Ne, Ar, Kr, etc., in the pressure range 10^{-4} to 10^{-3} Torr.

The change in capacitance of anodized pure aluminium layer due to sorption of moisture from air has been used to determine the relative humidity. Aluminium may be in the form of a small rod ($\frac{1}{16}$ in. diam. and $\frac{1}{2}$ in. length) or plate. Anodization forms, on the surface, a layer of about 25 μ thickness with a number of pores of diameter of the order of 500 A. The outer surface is coated with colloidal graphite particles so as to act as an electrode. Jason[89] discussed the origin, construction, theory, properties and application of this type of hygrometer. This type of apparatus makes it possible to investigate the microclimate and to make humidity measurements for inaccessible locations. According to Miyata and Watari[90], the porous anodized film acts as a dielectric and is apt to adsorb moisture from the ambient atmosphere. Ansbacher and Jason[91] discussed the effects of water vapour on the electrical properties of anodized aluminium. Cutting *et al.*[92] measured vapour pressure by noting changes in electrical properties of anodized aluminium oxide layer. The calibration is independent of temperature (0-80°C.) and air speed.

Spectroscopic Hygrometers

Infrared and ultraviolet radiation of certain wavelengths are attenuated proportional to water vapour

present in the atmosphere. This property is used to determine relative humidity or moisture in any ambient atmosphere. Foster *et al.*[93] compared the intensity of radiation in a selected region of absorption with that of another radiation having no absorption. Randall *et al.*[94] used a hydrogen lamp to produce a radiation of 1215·6 A. through a lithium chloride window. The radiation passes across a measuring path and through another lithium chloride window into a nitric oxide gas detector tube. Photo-ionization by this radiation causes a current to flow in the metering circuit associated with nitric oxide gas tube and this current is a function of water vapour density in the measuring path. Tank and Wergin[95] used a temperature compensated lead sulphide cell detector to sense the intensity. Silicon cells are also used as radiation detectors. The apparatus used by Tank and Wergin[95] has an accuracy of 0·5 per cent of the total humidity. Staats *et al.*[96] measured absolute humidity by measuring the absorption effected in the 1·37 μ water vapour absorption band. Wood[97] designed an infrared hygrometer which utilizes a light beam as the principal sensing element. It is composed of two narrow bands of infrared radiation. One band, centred near the wavelength 2·60 μ, is subjected to attenuation by water vapour, but the other, located near 2·45 μ, is not. Thus the ratio of transmitted band energies is sensitive to water vapour concentration variation.

Microwave Hygrometer

The refractive index of a medium changes with the density of the medium. The index can be measured by means of microwave. Sargent[98] designed a recording microwave hygrometer to measure vapour concentration. The difference between the refractive indices of dry and humid air is determined and converted into concentration of vapour. The sensitivity of the hygrometer is 0·004 mm. Hg up to 71·3 mm. Hg pressure in moving air stream. Magn and Crain[99] developed another recording microwave hygrometer, which involves the measurement of the contribution of water vapour to the refractive index of atmospheric air by a cavity resonator.

Sivadjian[100] designed a hygrophotographic hygrometer based on the sensitivity of a photochemical reaction accompanied by change of colouration which disappears instantaneously under the action of a small quantity of water or humidity. The hygrometer is particularly suitable for determining foliage transpiration, soil humidity, perspiration from skin, etc.

Summary

Recent advances in the measurement and control of vapour pressure of water and other liquids are reviewed. The principles, modes of working and special features of various types of instruments developed — psychrometers, dew point hygrometers, radiation manometers, heat of adsorption manometers, viscosity and diffusion manometers, electric hygrometers, electrolytic hygrometers, capacitance hygrometers, spectroscopic hygrometers, and microwave hygrometers — are discussed.

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References

1. Gregory, H. S. & Rourke, E., *Hygrometry* (Crosby Lockwood & Sons Ltd, London), 1957.
2. Nesmeyanov, A. N., *Vapour pressure of chemical elements* (Elsevier Publishing Co., New York), 1963.
3. Latham, J. & Stow, C. D., *J. scient. Instrum.*, **41** (1964), 324.
4. Rocha, M., *Proc. 4th intern. conf. soil mech. foundation engng* (Butterworths Scientific Publications Ltd, London), 1957.
5. Muller, H. G., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 574.
6. Iles, W. G. & Worsnop, K., *Proc. phys. Soc.*, **48** (1936), 358.
7. Davey, F. K., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 571.
8. Lebedeff, A. F., *Proc. first int. congr. soil sci.*, Vol. 1 (The American Organizing Committee of the First Int. Congr. of Soil Science, Washington DC), 1927, 459.
9. Shoemaker, D. P. & Garland, C. W., *Experiments in physical chemistry* (McGraw-Hill Book Co. Inc., New York), 1962.
10. Brown, R. C., *Mechanics and properties of matter* (Longmans Green & Co., London), 1950.
11. Borrell, P. & Nyburg, S. C., *J. chem. Educ.*, **42** (1965), 557.
12. Douslin, D. R. & Osborn, A., *J. scient. Instrum.*, **42** (1965), 369.
13. Fender, D. H., *General physics and sound* (English Universities Press Ltd, London), 1957.
14. Barrer, R. M. & Wasilewskai, S., *J. scient. Instrum.*, **37** (1960), 432.
15. Foord, S. G., *J. scient. Instrum.*, **11** (1934), 126.
16. Nelkon, M., *Mechanics and properties of matter* (William Heinemann Ltd, London), 1958.
17. Grotyohann, A. G., *Rev. scient. Instrum.*, **32** (1961), 345.
18. Newman, F. H. & Searle, W. H. L., *The general properties of matter* (Edward Arnold & Co., London), 1951.
19. Middleton, W. E. K. & Spilhaus, A. F., *Meteorological instruments* (University of Toronto Press), 1953.
20. Simons, A., *Proc. phys. Soc.*, **48** (1936), 135.
21. Powell, R. W., *Proc. phys. Soc.*, **48** (1936), 406.
22. Richardson, L., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 101.
23. Box (Jr), J. E., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 110.
24. Richards, L. A., *Chem. Abstr.*, **66** (1967), 5918.
25. Shiba, K. & Tozawa, T., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 64.
26. Worrall, R. W., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 105.
27. Branton, C. I., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 95.
28. Collins, B. G., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 83.
29. Taylor, R. J., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 76.
30. Bemis, A. C., *Compendium of meteorology* (American Meteorological Society, Massachusetts), 1951.
31. Paine, I. C. & Farrah, H. R., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 174.
32. Dobson, G. B. M. & Brewer, A. W., *Compendium of meteorology* (American Meteorological Society, Massachusetts), 1951.
33. Hartley, J. L., Chamberlin, J. L. & Huff, W. D., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 205.

34. WYLIE, R. G., DAVIES, D. K. & CAW, W. A., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 125.
35. BREWER, A. W., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 134.
36. JOHN, P. T. & SEKHON, R. S., *Indian J. Technol.*, **4** (1966), 78.
37. *Notes on applied science*, No. 4 (Her Majesty's Stationary Office), 1955.
38. JOHN, P. T. & SEKHON, R. S., *Indian J. pure appl. Phys.*, **3** (1965), 38.
39. THORNTHWAITE, C. W. & OWEN, J. C., *U.S. Mon. Weather Rev.*, **68** (1940), 315.
40. ARMSTRONG, V., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 202.
41. BALLINGER, J. G., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 189.
42. MARTIN, S., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 149.
43. KOBAYASHI, H., *Japan J. appl. Phys.*, **2** (1963), 592.
44. JOHN, P. T. & BADGLEY, F. I., *Proc. WSC hydraulics conf. and the 4th meeting of Pacific NW branch of Am. Geophys. Un.*, held at Pulman, Washington (Technical Extension Services, Washington State Institute of Technology, Washington State), 1957.
45. JOHN, P. T., *Indian J. pure appl. Phys.*, **1** (1963), 392.
46. MARTIN, S., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 144.
47. NATHAN, A. M., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 155.
48. FRANCISCO, C. C. & BEAUBIEN, D. J., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 165.
49. GRIFFIN, O. G. & STRINGFIELD, C. M., *J. scient. Instrum.*, **41** (1964), 241.
50. Cambridge Systems Inc., *Rev. scient. Instrum.*, **36** (1965), 1680.
51. BRENDENG, E., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 209.
52. FRASER, M. J. & WEART, H. W., *Rev. scient. Instrum.*, **32** (1961), 221.
53. DOBSON, G. M. B., BREWER, A. W. & CWILONG, B. M., *Proc. roy. Soc., Lond.*, **A185** (1946), 144.
54. Burton Manufacturing Co., *Rev. scient. Instrum.*, **28** (1957), 191.
55. BARROWS, A. W. & HOWARD, R. J., *Rev. scient. Instrum.*, **32** (1961), 1401.
56. ADAM, N. K., *Physical chemistry* (Oxford University Press, London), 1954.
57. DOWNES, J. G. & NORDON, P., *J. scient. Instrum.*, **40** (1963), 596.
58. FLUMERFELT, G. C., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 584.

58a. GREINACHER, cited in GREGORY, H. S. & ROURKE, E., *Hygrometry* (Crosby Lockwood & Sons Ltd, London), 1957, 201.

59. MORECROFF, D. W., *J. Inst. Petrol.*, **50** (1964), 490.
60. SILVA, W. J., JOHNSON, J. W. & CUBICCIOTTI, D., *Rev. scient. Instrum.*, **36** (1965), 1505.
61. SMITH, W. J. & HOEFLICH, N. J., *Bull. Am. met. Soc.*, **33** (1954), 60.
62. FUKUDA, H., *Soil Sci.*, **81** (1956), 2.
63. DUNMORE, F. W., *Bull. Am. met. Soc.*, **21** (1940), 249.
64. MATHEWS, D. A., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 219.
65. MATHEWS, D. A., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 228.
66. KOBAYASHI, J. & TOYAMA, Y., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 248.
67. HANDEGORD, G. O. & TILL, C. E., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 280.
68. ROGERS, M. N., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 302.
69. HEDLIN, C. P. & TROFIMENKOFF, F. N., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 627.
70. SZALAI, L., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 298.
71. BRASTAD, W. A. & BORCHARDT, L. F., *Rev. scient. Instrum.*, **24** (1952), 1143.
72. JOHNSON, C. E. & DUGGAN, S. R., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 358.
73. JONES, F. E., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 361.
74. MUSA, R. C. & SCHNABLE, G. L., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 346.
75. WYLIE, R. G., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 606.
76. KING (Jr), W. H., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 578.
77. STINE, S. L., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 316.
78. CZUHA (Jr), M., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 522.
79. JONES, R. H. & PETERSEN, A., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 507.
80. MACCREADY (Jr), P. B. & LAKE, J. A. K., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 512.
81. CRAWSHAW, J. K. & DAVIDSON, F. G., *J. scient. Instrum.*, **36** (1959), 121.
82. MORRIS, V. B. & SOBEL, F., *Bull. Am. met. Soc.*, **35** (1954), 226.
83. GOLDSMITH, P. & COX, L. C., *J. scient. Instrum.*, **44** (1967), 29.
84. GRAY, P. S. & GORDON, I., *J. scient. Instrum.*, **44** (1967), 84.
85. UNDERWOOD, C. R. & HOUSLIP, R. C., *J. scient. Instrum.*, **32** (1955), 432.
86. NELSON, D. E. & AMDUR, E. J., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 597.
87. CHARLSON, R. J., *Science, N.Y.*, **143** (1964), 1031.
88. UTTERBACK, N. G. & GRIFFITHS (Jr), T., *Rev. scient. Instrum.*, **37** (1966), 866.
89. JASON, A. C., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 372.
90. MIYATA, A. & WATARI, H., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 391.
91. ANSBACHER, F. & JASON, A. C., *Nature, Lond.*, **171** (1953), 177.
92. CUTTING, C. L., JASON, A. C. & WOOD, J. L., *J. scient. Instrum.*, **32** (1955), 425.
93. FOSTER, N. B., WOLZ, D. T. & FOSKETT, I. W., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 455.
94. RANDALL, D. L., HANLEY, T. E. & LARISON, O. K., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 444.
95. TANK, W. J. & WERGIN, E. J., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 481.
96. STAATS, W. F., FOSKETT, L. W. & JENSEN, H. P., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 465.
97. WOOD, R. C., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 492.
98. SARGENT, J., *Rev. scient. Instrum.*, **30** (1959), 348.
99. MAGN, J. B. & CRAIN, C. M., *Rev. scient. Instrum.*, **29** (1958), 51.
100. SIVADJIAN, M. J., *Humidity and moisture*, edited by A. Wexler, Vol. 1 (Reinhold Publishing Corp., New York), 1965, 656.

Rauwolfia Alkaloids in Retrospect*

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THE genus *Rauwolfia* belonging to the subfamily Plumeroideae is an important member of the family Apocynaceae. It was so named in 1703 by Plumier[1], the pioneer Carribean botanist, after Leonhart Rauwolf (Leonardus Rauvolfius), a sixteenth century German botanist and physician. Although the correct name should have been *Rauvolfia* according to the International Code of Botanical Nomenclature, the popularity of the name *Rauwolfia* is too great to be corrected at this stage.

A comprehensive list of about 150 species of *Rauwolfia* with their habitat collected from the supplements of Index Kewensis has already been recorded in two earlier reviews[2,3] on the subject. However, in an excellent treatise, Woodson *et al.*[4] listed about 86 distinctly recognizable species of *Rauwolfia* growing in almost all the tropical and subtropical regions of the globe. The height varies from six inches of a rhizomatous sub-shrub of Rhodesia, viz. *R. nana*, to over a hundred feet tall tree, namely *R. praecox*, of Peru.

The use of the root preparations of *R. serpentina* was known from very ancient times as a remedy for snake-bite, insanity, etc. The old practice of putting children to sleep or keeping them quiet with this drug evidently shows the early knowledge of a section of Indian people about its hypnotic property. No serious pharmacological or chemical investigation of this 'insanity root', as it commonly became known in Europe in the sixteenth century for its reported use against mental disorder, was, however, attempted till 1930. Siddiqui and Siddiqui[5] appear to be the first to examine the roots of *R. serpentina* Benth. chemically in 1931. It is interesting to note here that ajmaline (neoajmaline)[5-7], ajmalinine, ajmalicine[5] and isoajmaline[8] were named after Hakim Ajmal Khan, the founder of the Research Institute, A.U. Tibbi College, Delhi. The remarkable researches initiated by Chopra and his collaborators during 1933-43 on the pharmacological basis of the hypotensive and sedative activities of the root alkaloids of *R. serpentina* have been ably summarized by Werner *et al.*[3].

When Siddiqui isolated those alkaloids from *R. serpentina* or when Chatterjee (*née* Mookerjee) isolated[9] rauwolscine (α-yohimbine[10]) from *R. canescens*, they hardly could imagine that these two low shrubs growing wildly in India would attain such a stature and stir the whole medical and chemical professions that they did with the isolation of reserpine, the highly potent hypotensive and tranquillizing agent, by Mueller *et al.*[11]. The tremendous enthusiasm aroused by this discovery resulted in the investigations of about 50 species of *Rauwolfia* yielding more than equal number of alkaloids. Only three species, namely *R. serpentina* and *R. canescens* of Indian origin and *R. vomitoria* of Central Africa (Congo), are, however, important commercially. Again, the reserpine content of *R. vomitoria* is twice as much as that of *R. serpentina* and is considered to be the richest source of this drug known so far. Although the glamour of this field waned considerably with the brilliant synthesis of reserpine by Woodward and his collaborators[12], interest in the field still continues. Modification of the reserpine structure with a view to separating its principal pharmacological properties, namely the hypotensive and tranquillizing effects, or to avoid the undesirable side effects have been sought and to some extent achieved[13]. A voluminous literature thus accumulated, necessitating a number of unusually frequent reviews[2-4,13-21] on the subject. In the present article, therefore, it is intended to deal with the general physico-chemical characteristics, the important structural features and the general approach to their elucidation, stereochemistry and biogenesis of *Rauwolfia* alkaloids rather than to detail the investigations on any of the individual alkaloid. The literature coverage in this review is essentially complete through 1966.

Classification

Alkaloids (I-XIX) with five types of basic chromophoric systems, viz. (i) indole (including extended conjugation in case of anhydronium bases), (ii) indoline, (iii) indolenine, (iv) oxindole, and (v) Ψ-indoxyl, have been isolated from the *Rauwolfia* species exmined so far. The previous classifications[3,4,17] based on different chromophoric systems had to be modified[18-20] because of the occurrence of alkaloids of ajmaline-like caged-ring structures embodying all but oxindole and Ψ-indoxyl chromophores.

We have sought to classify (Table 1) the known *Rauwolfia* alkaloids broadly according to the chromophoric systems and to subdivide them under their gross skeletal structures. The synonyms of both the alkaloids and species have deliberately been excluded to avoid further confusion in the literature although the relevant references are recorded against the accepted nomenclatures. It is also worth while to consult other monographs[20,116].

Reserpine is the most widespread *Rauwolfia* alkaloid found in all but the species *R. beddomei*, *R. degeneri*, *R. fruticosa*, *R. mauiensis*, *R. semperflorens* and *R. verticillata*. Rescinnamine and reserpiline, the next abundant alkaloids, are found mostly to occur with reserpine. Their common sources are: *R. bahiensis*, *R. caffra*, *R. cubana*[20,45], *R. densiflora*[70], *R. grandiflora*, *R. lamarckii*, *R. littoralis*[20,45], *R. lingustrina*[20,29,45], *R. mombasiana*, *R. nitida*, *R. paraensis*, *R. pentaphylla*, *R. salicifolia*, *R. sprucei*[20,45], *R. serpentina*[64,114], *R. sumatrana*[20,45] and *R. vomitoria*[35,115]. Their sources other than these are enlisted in Table 1.

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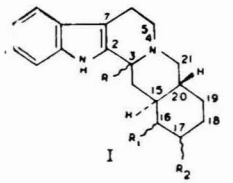
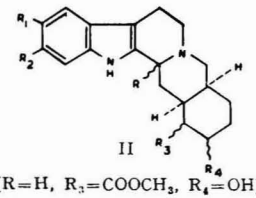


I

[R=H, R_1=$COOCH_3$, R_2=OH]

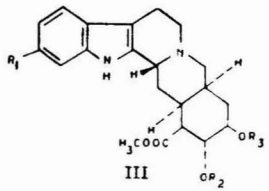
a, Yohimbine, R, R_1, R_2=α
b, β-Yohimbine, (a) but R_2=β
c, ψ-Yohimbine, (a) but R=β
d, Corynanthine, (a) but R_1=β



II

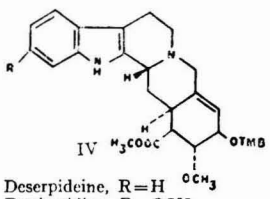
[R=H, R_3=$COOCH_3$, R_4=OH]

a, α-Yohimbine, R_1=R_2=H; R, R_4=α; R_3=β
b, 3-epi-α-Yohimbine, (a) but R=β
c, Seredine, (a) with R_1=R_2=OCH_3



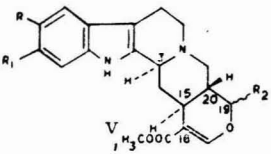
III

a, Raunescine, R_1=R_2=H; R_3=TMB*
b, Isoraunescine, R_1=R_3=H; R_2=TMB
c, Deserpidine, (a) but R_2=CH_3
d, Reserpic acid methyl ester, R_1=OCH_3; R_2=CH_3; R_3=H
e, ψ-Reserpine, R_1=OCH_3; R_2=H; R_3=TMB
f, Iso-ψ-reserpine†, R_2=TMB; R_3=H; R_1=OCH_3
g, Reserpine, (e) except R_2=CH_3
h, Isoreserpine, (g) except C_3-H=α
i, Raugustine, (d) but R_2=TMB
j, Rescidine, (e) except R_3=TMC‡
k, Rescinnamine, (j) except R_2=CH_3
l, Renoxydine, Reserpine-N_b-oxide



IV

a, Deserpideine, R=H
b, Raujemidine, R=OCH_3

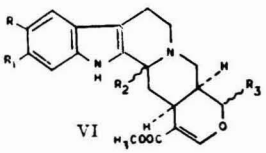


V

[R_2=CH_3]

a, Ajmalicine, R=R_1=H; R_2=α
b, Tetraphylline, R=H; R_1=OCH_3; R_2=α
c, Raumitorine, R=OCH_3; R_1=H; R_2=β
d, Rauvanine, R=R_1=OCH_3; R_2=β

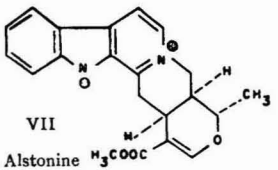
*TMB=3,4,5-trimethoxy benzoyl
†Stereochemistry is not implied
‡TMC=3,4,5-trimethoxy cinnamoyl



VI

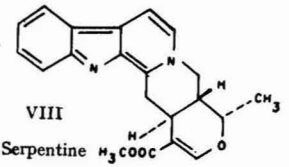
[R_2=H, R_3=CH_3]

a, Tetrahydroalstonine, R=R_1=H; R_2, R_3=α
b, Rauniticine, R=R_1=H; R_2=α; R_3=β
c, Reserpinine, (a) but R_1=OCH_3
d, Isoreserpinine, R=H; R_1=OCH_3; R_2=β; R_3=α
e, Raunitidine, (b) but R_1=OMe
f, Aricine, R=OCH_3; R_1=H; R_2, R_3=β
g, Reserpiline, (d) but R=OCH_3
h, Isoreserpiline, (a) but R=R_1=OCH_3



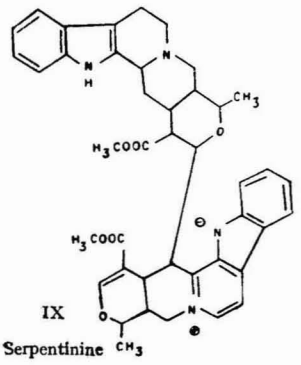
VII

Alstonine



VIII

Serpentine



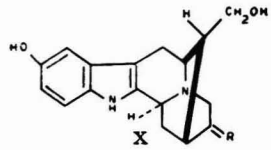
IX

Serpentinine

Ultraviolet Spectra

Sangster and Stuart[117] have recently reviewed the UV spectra of alkaloids including indole derivatives. They have shown that unsubstituted indole alkaloids generally show two distinct peaks, one at 226-228 mμ and the other at 280-292 mμ. Substitution in the aromatic ring affects the UV spectra, usually leading to a bathochromic shift of the long wavelength maximum depending on the number of substituents. For example, the maximum at 291 mμ in tetrahydroalstonine (VIa) and ajmalicine (Va) is shifted to 296 mμ in the corresponding C_{11}-methoxylated compounds, viz. reserpinine (VIc) and tetraphylline (Vb) and to 304 mμ in 10,11-dimethoxylated compound, e.g. isoreserpiline (VIh). In reserpine and its analogues, however, a composite spectrum of indole and trimethoxybenzoic acid chromophores is observed. Deserpidine (IIIc), for instance, absorbs at 216, 271 and 289 mμ while substitution of ring A affects the longer wavelength maximum in the same way. Introduction of an unconjugated double bond in this system as in 19-dehydro compounds does not influence the absorption maxima.

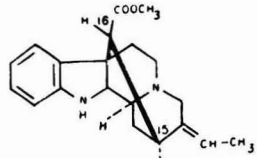
The salts of anhydronium bases embodying in fact a β-carbolinium chromophore exhibit three distinct peaks approximately at 252, 308 and 370 mμ. A large bathochromic shift of the maxima, particularly of the one in the longer wavelength region, has been noted in the corresponding bases. A strong absorption at around 250 mμ characterizes the presence of a $CH_3OOC-C=C-O-$ chromophoric system in these and other heteroyohimbine bases. For the combination of indole and β-carbolinium chromophores in serpentinine (IX), the characteristic peaks for both the systems appear at 227, 257, 281, 294, 308 and 373 mμ. It is remarkable that on the basis of these UV data Djerassi *et al.*[40] could foresee the possibility of such a structure for this alkaloid.



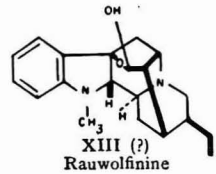
X

Neosarpagine, R = CH=CH$_2$ / H

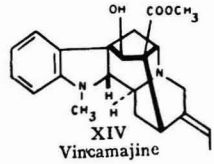
Sarpagine, R = CH–CH$_3$



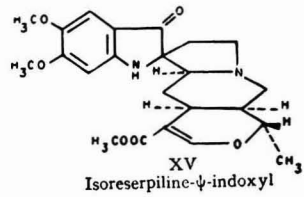
XII
Picrinine



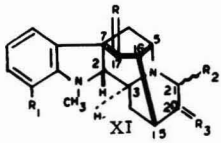
XIII (?)
Rauwolfinine



XIV
Vincamajine



XV
Isoreserpiline-ψ-indoxyl



XI

a, Ajmaline, R = OH / H, R_1=H;
R_2=OH, α; R_3 = C_2H_5 / H

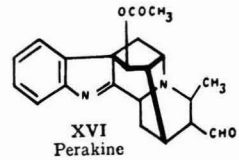
b, Isoajmaline; (a) but R_3 = C_2H_5 / H

c, Sandwicine, (a) but R = OH / H

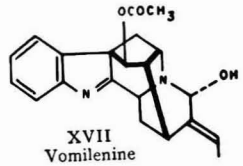
d, Ajmalidine, (a) but R = O
e, Vomalidine, C_{11}-OCH_3 derivative of (d)

f, Tetraphyllicine, R = OH / H

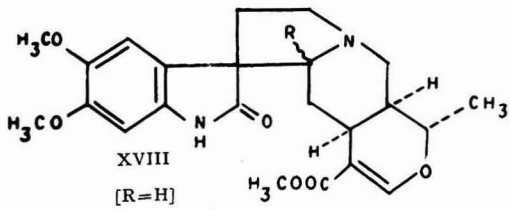
R_1=R_2=H; R_3=CH–CH_3
g, Mauiensine, C_{17} epimer of (f)
h, Rauvomitine, TMB ester of (f)
i, Mitoridine, R = O; R_1 = OH; R_2=H; R_3=CH–CH_3
j, Purpeline, (i) but R_1 = OCH_3
k, Seredamine, (f) but R_1 = OCH_3



XVI
Perakine

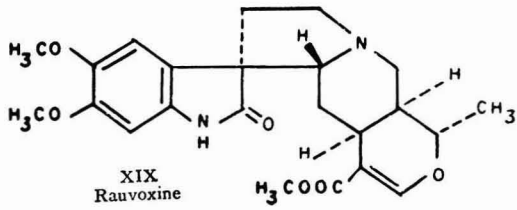


XVII
Vomilenine



XVIII
[R=H]

a, Carapanaubine, R=α
b, Rauvoxinine, R=β



XIX
Rauvoxine

The indoline alkaloids are characterized by distinct bands at around 250±2 and 290±5 mμ which remain unaffected by acid treatment. Though substitution on the aromatic ring is expected to affect the UV spectrum[118,119], vomalidine (XIe), the only such compound known to occur in *Rauwolfia* species, does not show[110] any appreciable shift (λmax. 253, 292 mμ). Vomilenine (XVII), the indolenine derivative, exhibits two maxima at 218 and 257 mμ, typical of this chromophoric system.

The known oxindole alkaloids from *Rauwolfia* are disubstituted in the aromatic ring. They show[110] two common peaks of almost equal intensity at 213-215 and 296-300 mμ. The position and the intensity of the third peak distinctly vary with the stereochemistry at the C_3 centre. A maximum observed at 244 mμ (ε = 11,950) for compounds having α-oriented C_3-H is shifted to 275 mμ (ε ~ 6000) in their C_3-epimers. Isoreserpiline-Ψ-indoxyl (XV)[77], the only of its kind encountered in this genus, exhibits peaks at 251, 283 and 405 mμ though the Ψ-indoxyls are expected to absorb[120] at 235 and 400 mμ.

Infrared Spectra

An excellent compilation[110] of the IR spectra of the *Rauwolfia* alkaloids along with the UV and X-ray powder data is available. Neuss and Boaz[121] first attempted with remarkable success the correlation of the IR spectra particularly of the heteroyohimbine bases with their stereochemistry. It was at least possible to relate the stereochemistry of

TABLE 1 — ALKALOIDS OF *Rauwolfia* SPECIES

Sl No.	Name	Mol. formula	m.p. °C.	$[\alpha]_D^*$	Source
			INDOLE ALKALOIDS: (a) Yohimbine type		
1	Canembine (?)†	$C_{22}H_{28}N_2O_3$	228-9	+57° (Ethanol)	*canescens*[22]
2	Corynanthine (Id)	$C_{21}H_{26}N_2O_3$	231-2	−85° (Pyridine)	*canescens*[23], *serpentina*[24]
3	Seredine (IIc)	$C_{23}H_{30}N_2O_5$	291	−1°	*vomitoria*[25]
4	Yohimbine (Ia)	$C_{21}H_{26}N_2O_3$	234-6	+101° (Pyridine)	*amsoniaefolia*[26], *canescens*[27], *fruticosa*[28], *lingustrina*[29], *serpentina*[30,52], *sumatrana*[31], *tetraphylla*[32], *vomitoria*[33]
5	α-Yohimbine (IIa)	$C_{21}H_{26}N_2O_3$	238-9	−12°	*canescens*[9], *lingustrina*[29], *serpentina*[34], *sumatrana*[31], *tetraphylla*[35,36], *vomitoria*[33]
6	β-Yohimbine (Ib)	$C_{21}H_{26}N_2O_3$	246-9	−54° (Pyridine)	*canescens*[37]
7	3-*epi*-α-yohimbine (IIb)	$C_{21}H_{26}N_2O_3$	125-8 181-3 222-3	−93°	*serpentina*[24,38]
8	Ψ-Yohimbine (Ic)	$C_{21}H_{26}N_2O_3$	268	+27° (Pyridine)	*canescens*[39], *tetraphylla*[40]
			(b) 18-Hydroxy-yohimbine type		
9	Deserpidine (IIIc)	$C_{32}H_{38}N_2O_8$	228-32	−137°	*amsoniaefolia*[26], *canescens*[22,23,41-44], *cubana*, *grandiflora*, *javanica*[20,45], *lingustrina*[20,23,45], *littoralis*, *salicifolia*, *sprucei*, *tetraphylla*[20,45]
10	Isopseudoreserpine (IIIf)	$C_{32}H_{38}N_2O_9$	—	—	*lingustrina*[46]
11	Isoraunescine (IIIb)	$C_{31}H_{36}N_2O_8$	241-2	−70°	*canescens*[47], *lingustrina*[29]
12	Isoreserpine (IIIh)	$C_{33}H_{40}N_2O_9$	152-6	−164°	*lingustrina*[29]
13	Raugustine (IIIi)	$C_{32}H_{38}N_2O_9$	160-70	−50°	*grandiflora*[48], *lingustrina*[29,48], *mattfeldiana*[48]
14	Raunescine (IIIa)	$C_{31}H_{36}N_2O_8$	160-70	−74°	*canescens*[47], *grandiflora*[48], *lingustrina*[29,48], *tetraphylla*[49]
15	Renoxidine (IIIl)	$C_{33}H_{40}N_2O_{10}$	238-41	−100°	*canescens*[50], *lingustrina*[29], *serpentina*, *vomitoria*[50]
16	Rescidine (IIIj)	$C_{34}H_{40}N_2O_9$	183-6	−63°	*vomitoria*[51]
17	Rescinnamine (IIIk)	$C_{35}H_{42}N_2O_9$	237-8	−97°	*amsoniaefolia*[26], *caffra*, *obscura*[20,45]
18	Reserpic acid methyl ester (IIId)	$C_{23}H_{30}N_2O_5$	244-5	−99°	*amsoniaefolia*[26], *serpentina*[52]
19	Reserpine (IIIg)	$C_{33}H_{40}N_2O_9$	264-5	−117°	see text
20	Ψ-Reserpine (IIIe)	$C_{32}H_{38}N_2O_9$	257-8	−65°	*canescens*[53], *grandiflora*[48], *lingustrina*[29], *mattfeldiana*[48], *tetraphylla*[49]
			(c) 19-Dehydro-18-hydroxy-yohimbine type		
21	Deserpideine (IVa)	$C_{32}H_{36}N_2O_8$	149-52	−133° (Pyridine)	*nitida*[54]
22	Raujemidine (IVb)	$C_{33}H_{38}N_2O_9$	144-50	−88°	*canescens*[55]
			(d) Heteroyohimbine type		
23	Ajmalicine (Va)	$C_{21}H_{24}N_2O_3$	253-4	−62°	*amsoniaefolia*[26], *beddomei*[56], *caffra*[20,45], *canescens*[23,57], *fruticosa*[31], *grandiflora*[20,45], *javanica*[58], *lingustrina*[29], *micrantha*[59], *nitida*[60], *pentaphylla*, *rosea*, *sandwicensis*[20,45], *sellowii*[61], *serpentina*[5,27,62-64], *sumatrana*[28], *verticillata*[65,66]
24	Aricine (VIf)	$C_{22}H_{28}N_2O_4$	190	−59° (Ethanol)	*amsoniaefolia*[26], *canescens*[67], *lingustrina*[29], *nitida*[60], *schueli*[68], *sellowii*[61], *sumatrana*[31], *tetraphylla*[35]
25	Isoreserpiline (VIh)	$C_{23}H_{28}N_2O_5$	211-2	−82° (Pyridine)	*cambodiana*[69], *canescens*[67], *densiflora*[70], *lamarckii*[20,45], *lingustrina*[29], *nitida*[60], *perakensis*[71], *salicifolia*[20,45], *schueli*[68], *sprucei*[20,45], *tetraphylla*[49], *vomitoria*[72]
26	Isoreserpinine (VId)	$C_{22}H_{26}N_2O_4$	225-6	−18°	*canescens*[67], *lingustrina*[29], *nitida*[60]
27	Rauniticine (VIb)	$C_{21}H_{24}N_2O_3$	233-5	−38°	*nitida*[60]
28	Raunitidine (VIe)	$C_{22}H_{26}N_2O_4$	276-8	−70°	*nitida*[60]
29	Raumitorine (Vc)	$C_{22}H_{26}N_2O_4$	138	+60°	*vomitoria*[25]
30	Rauvanine (Vd)	$C_{23}H_{28}N_2O_5$	129-35	+32°	*vomitoria*[73]
31	Reserpiline (VIg)‡	$C_{23}H_{28}N_2O_5$	—	−12°	*canescens*[67], *discolor*[74], *grandiflora*, *mattfeldiana*[48], *micrantha*[59,75], *rosea*, *sandwicensis*[20,45], *schueli*[68,71]
32	Reserpinine (VIc)	$C_{22}H_{26}N_2O_4$	243-4	−131°	*canescens*[67], *densiflora*[70,76], *discolor*[74], *grandiflora*, *lamarckii*, *lingustrina*[20,45], *nitida*[60], *pentaphylla*[20,45], *serpentina*[27,52,62,64,76], *tetraphylla*[20,45]
33	Tetrahydroalstonine (VIa)	$C_{21}H_{24}N_2O_3$	228-30	−102°	*lingustrina*[29], *sellowii*[61]
34	Tetraphylline (Vb)	$C_{22}H_{26}N_2O_4$	220-3	−78°	*discolor*[74], *nitida*[20,45], *sandwicensis*[78], *tetraphylla*[79]
			(e) Anhydronium type		
35	Alstonine (VII)	$C_{21}H_{20}N_2O_3$	300	—	*obscura*[80], *tetraphylla*[36], *vomitoria*[80]
36	Serpentine (VIII)	$C_{21}H_{20}N_2O_3$	158	+292° (Methanol)	*beddomei*[81], *canescens*[27], *fruticosa*[28], *javanica*[58], *lingustrina*[29], *micrantha*[59], *sellowii*[61,81], *serpentina*[5], *sumatrana*[31], *tetraphylla*[82,83]
37	Serpentinine (IX)‡	$C_{42}H_{44}N_4O_6$	265-6	+117°	*javanica*[58], *lingustrina*[29], *mauiensis*[78], *sandwicensis*[78], *serpentina*[5], *tetraphylla*[79], *vomitoria*[84]

TABLE 1 — ALKALOIDS OF *Rauwolfia* SPECIES — *Contd*

Sl No.	Name	Mol. formula	m.p. °C.	$[\alpha]_D^*$	Source
			(f) Sarpagine type		
38	Neosarpagine (Xa)	$C_{19}H_{22}N_2O_2$	390	—	*micrantha*[85]
39	Sarpagine (Xb)	$C_{19}H_{22}N_2O_2$	350	+53° (Pyridine)	*beddomei*[56], *canescens*[23], *densiflora*[70,76], *javanica*[58], *lingustrina*[29,32], *micrantha*[86], *perakensis*[71], *serpentina*[87,88], *sumatrana*[89], *tetraphylla*[32,36], *vomitoria*[72]
			INDOLINE ALKALOIDS: Ajmaline type		
40	Ajmalidine (XId)	$C_{20}H_{24}N_2O_2$	241-2	—	*mauiensis*[90], *sellowii*[61]
41	Ajmaline (XIa)	$C_{20}H_{26}N_2O_2$	158-60	+141°	*caffra*[91,92], *canescens*[23], *densiflora*[93], *fruticosa*[31], *javanica*[58], *lingustrina*[29,32], *micrantha*, *mombasiana*[91], *nana*[94], *obscura*[95], *perakensis*[71], *sandwicensis*[78], *schueli*[68,71], *sellowii*[61], *serpentina*[5], *sumatrana*[31], *vomitoria*[84], *verticillata*[66]
42	Mauiensine (XIg)	$C_{20}H_{24}N_2O$	240-2	+184° (Methanol)	*mauiensis*[78]
43	Isoajmaline (XIb)	$C_{20}H_{26}N_2O_2$	264-6	+72°	*serpentina*[8], *vomitoria*[84]
44	Mitoridine (XIi)	$C_{20}H_{22}N_2O_2$	322	+175° (Pyridine)	*vomitoria*[96]
45	Picrinine (XII)	$C_{20}H_{22}N_2O_2$	216	—	*vomitoria*[97]
46	Purpeline (XIj)	$C_{21}H_{24}N_2O_2$	155	+333°	*vomitoria*[96]
47	Rauvomitine (XIh)	$C_{30}H_{34}N_2O_5$	115-17	−173°	*vomitoria*[98]
48	Rauwolfinine (XIII)	$C_{20}H_{26}N_2O_2$	235-6	−35° (Ethanol)	*perakensis*[93], *serpentina*[99]
49	Sandwicine (XIc)	$C_{20}H_{26}N_2O_2$	—	+180°	*mauiensis*, *sandwicensis*[78]
50	Seredamine (XIk)	$C_{21}H_{26}N_2O_2$	297	+60°	*vomitoria*[96]
51	Tetraphyllicine (XIf)	$C_{20}H_{24}N_2O_2$	320-2	+61°	*mauiensis*[78], *obscura*[95], *sandwicensis*[78], *sellowii*[61], *serpentina*[100], *tetraphylla*[79]
52	Vincamajine (XIV)	$C_{22}H_{26}N_2O_3$	225	−55° (Ethanol)	*manii*[101]
53	Vomalidine (XIe)	$C_{21}H_{26}N_2O_3$	242-3	+318°	*vomitoria*[102]
			Ψ-INDOXYL ALKALOID		
54	Isoreserpiline-Ψ-indoxyl (XV)	$C_{23}H_{28}N_2O_6$	252-4	−254°	*lingustrina*[103], *vomitoria*[77]
			INDOLENINE ALKALOIDS		
55	Perakine (XVI)§	$C_{21}H_{22}N_2O_3$	183	+112°	*caffra*[101], *perakensis*[71], *vomitoria*[105]
56	Vomilenine (XVII)	$C_{21}H_{22}N_2O_3$	207	−72° (Pyridine)	*vomitoria*[106]
			OXINDOLE ALKALOIDS		
57	Carapanaubine (XVIIIa)	$C_{23}H_{28}N_2O_6$	221-3	−101°	*vomitoria*[107]
58	Rauvoxine (XIX)	$C_{23}H_{28}N_2O_6$	210	+98°	*vomitoria*[107]
59	Rauvoxinine (XVIIIb)	$C_{23}H_{28}N_2O_6$	203	+64°	*vomitoria*[107]
			ALKALOIDS OF UNKOWN STRUCTURE		
60	Ajmalinine¶	$C_{20}H_{26}N_2O_3$	180-1	−97°	*sellowii*[81], *serpentina*[5], *vomitoria*[84]
61	Alkaloid A	—	140	+133°	*vomitoria*[97]
62	Alkaloid D	—	184	+44°	*vomitoria*[97]
63	Alkaloid RP1	$C_{22}H_{26}N_2O_4$	—	—	*perakensis*[71]
64	Alkaloid RP2	$C_{24}H_{28}N_2O_4$	—	—	*perakensis*[71]
65	Alkaloid RP3	$C_{24}H_{32}N_2O_6$	—	—	*perakensis*[71]
66	Amsoniaefoline	$C_{25}H_{32}N_2O_5$	220-3	—	*amsoniaefolia*[108]
67	An alkaloid	$C_{14}H_{16}N_2$	190-2	−132° (?)	*canescens*[23]
68	Chandrine	$C_{23}H_{30}N_2O_8$(?)	230-1	—	*serpentina*[109]
69	Neoreserpiline	$C_{23}H_{28}N_2O_5$	129-31	−78° (Ethanol)	*perakensis*[110]
70	Obscuridine	—	228	—	*obscura*[95]
71	Obscurine	—	255	+250°	*obscura*[95]
72	Pelirine	$C_{21}H_{28}N_2O_4$	130-1	−121° (Ethanol)	*perakensis*[71]
73	Raucaffricine	$C_{26}H_{24}N_2O_8$	220	+14·5° (Ethanol)	*caffra*[104]
74	Raucaffridine	$C_{21}H_{24}N_2O_3$	221	—	*caffra*[104]
75	Raucaffriline	$C_{21}H_{22}N_2O_3$	200-1	—	*caffra*[104]
76	Raunamine	$C_{23}H_{30}N_2O_4$	206-7	+60°	*micrantha*[85]
77	Rauwolfine	$C_{20}H_{26}N_2O_3$	235-6	—	*caffra*[111]
78	Sandwicensine	$C_{19}H_{22}N_2O$	260-2	+56° (Methanol)	*sandwicensis*[78]
79	Samatine	$C_{21}H_{32}N_2O_7$	284-5	—	*verticillata*[112]
80	Semperflorine¶	$C_{21}H_{26}N_2O$	295	—	*semperflorens*[113]

*Unless otherwise mentioned, rotations were measured in chloroform.

†The structure is yet to be established. The proposed[22] 19-methyl α- or *allo*-yohimbine structure is doubtful.

‡Micranthine and serpentidine reported by Shavel *et al.*[59] are identical[20] respectively with reserpiline and serpentinine.

§Perakine appears to be an artefact of the isomeric vomilenine (XVII) since the latter can be converted to the former by boiling with 10 per cent acetic acid for 10 min.[106].

¶The identity of ajmalinine with 3-*epi*-α-yohimbine and that of semperflorine with tetraphyllicine cannot rigorously be excluded.

the methoxylated derivatives to either tetrahydroalstonine (VIa) or ajmalicine (Va) series. Thus, the positions and intensities of almost all the IR bands of reserpinine (VIc) exactly corresponded with those of the summation spectrum of an equimolar solution of 2,3-dimethyl-6-methoxyindole and tetrahydroalstonine. The nature of the ester band was also shown to be diagnostic in this respect. The ajmalicine type compounds exhibited a relatively simple ester band at 8·45 μ; in tetrahydroalstonine series this band was found to be distinctly resolved at 8·15, 8·32 and 8·45 μ. Reserpiline (VIg) and isoreserpiline (VIh) showed a broad band at 8·26 μ instead and the pattern of their IR spectra in general was distinct from either of the two types mentioned. The wavelength of the C=C band also varied according to stereochemical differences. For example, this band appeared at 6·1 μ for tetrahydroalstonine and at 6·19 μ for ajmalicine type. An intense band in the region 6·6-6·8 μ (calculated from the published spectra) was assigned to the methoxyl group substituted in the aromatic ring of the indole moiety.

Although the interpretations of the configurational assignments at the D/E ring junctions of these alkaloids were later proved to be untenable by Shamma and Moss[122], this approach still retains its usefulness for gross structural informations.

Wenkert and Roychaudhuri[123] almost simultaneously observed that the C-H stretching vibration at 3·4-3·7 μ region could be utilized for the determination of the configuration of the C_3-H of the *Rauwolfia* alkaloids. For example, compounds like yohimbine (Ia), α-yohimbine (IIa), etc., having α-oriented C_3-H, irrespective of the stereochemistry at D/E ring junctions, show multiple distinct and characteristic peaks of medium intensity in this region. On the other hand, those with β-oriented C_3-H, e.g. Ψ-yohimbine (Ic), 3-*epi*-α-yohimbine (IIb), etc., exhibit only shoulders on the high wavelength side of the main peak. Reserpine and its analogues, however, show a clear peak instead.

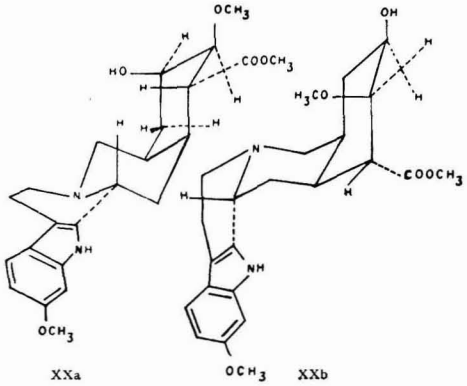
It is at least evident that the IR spectra allow classification of yohimbine and heteroyohimbine alkaloids into distinct stereochemical groups. Nevertheless, the assignment of configuration to the C_3-H on the basis of IR is not unambiguous in all cases[124].

Nuclear Magnetic Resonance Spectra

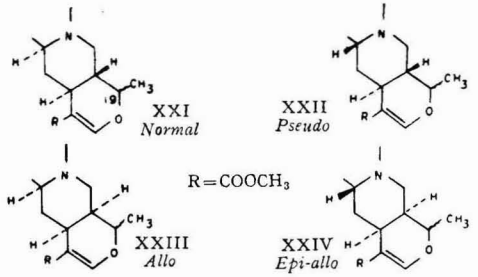
Albright *et al.*[125] observed that it is possible to differentiate the stereochemistry of C_{17}-OH group in yohimbine and its congeners. The equatorial C_{17}-proton signal, for example, in yohimbine, Ψ-yohimbine and corynanthine appears between $\delta = 4{\cdot}18$ and 3·98. The axial proton signal, both in α- and β-yohimbines, is shifted up field and a four-proton intensity peak at $\delta = 3{\cdot}73$ is observed due to overlapping by the methyl protons of the C_{16}-carbomethoxyl group. Acylation of the C_{17}-OH results in the down field shift of these signals, viz. the C_{17}-proton signal of the O-tosylates of yohimbine and β-yohimbine appears at $\delta = 5{\cdot}22$ and 4·83 respectively. The doublet at $\delta = 4{\cdot}88$-4·33, when measured in deuterodimethylsulphoxide instead of deuterochloroform, has been assigned to the hydroxyl-proton spin-coupled with the adjacent C_{17}-proton. Ψ-Yohimbine, however, showed a two-proton multiplet centred round $\delta = 4{\cdot}33$ — one due to hydroxyl and the other assigned to the equatorial (with respect to ring D) C_3-proton. A single-proton down field signal at $\delta = 4{\cdot}45$ assigned to equatorial C_3-H has also been noted for methyl reserpate and reserpine[126] and as such appears to be diagnostic[127].

An interesting application of NMR has been reported by Rosen and Shoolery[126] in the conformational studies on some 18-hydroxy-yohimbines. Methyl reserpate (IIId) having equatorial C_3-H and axial hydrogens at C_{16}, C_{17} and C_{18}, when refluxed with methanolic sodium methoxide under equilibrating conditions, is partly converted to methyl neoreserpate[128]. The latter can have two alternative conformations. In the more stable one (XXa), hydrogen is axial at C_3, C_{16} and C_{17} and equatorial at C_{18} while in the other (XXb) the assignment is just the opposite. Methyl neoreserpate exhibited a quartet at $\delta = 4{\cdot}21$ which showed a large down field shift to $\delta = 5{\cdot}78$ in its C_{18}-trimethoxybenzoate. The intensity distribution of 1-3-3-1 and the coupling constants of 2-3 cps in both the cases are compatible with the equatorial nature of C_{18}-H having small and almost equal spin coupling to three neighbouring protons. Those with axial C_{18}-H with its two axial and one equatorial neighbours (e.g. IIId) would also be expected to show far enough down field shift on similar acylation and peak centred around $\delta = 5{\cdot}08$ could be observed while the signal at $\delta = 4{\cdot}45$ for the equatorial C_3-H remained unaffected. The axial C_{18}-proton in methyl reserpate and its C_3-epimer could be inferred by the absence of the peak around $\delta = 5{\cdot}08$ in their spectra. Thus conformation (XXa) was assigned to methyl neoreserpate.

Again, the signal for the methyl protons of the equatorial C_{17}-OCH_3 group of 18-hydroxy-yohimbines is dependent on the orientation of the neighbouring groups. When both the carbomethoxyl and hydroxyl functions are equatorial, e.g. in methyl reserpate (IIId), this signal appears at $\delta = 3{\cdot}53$-3·60, which is shifted slightly to higher field ($\delta = 3{\cdot}41$) if one of them is axial (as in XXa). The methyl protons at C_{17} do not, however, exert significant vicinal effect on the peak positions ($\delta = 3{\cdot}80$-3·87) of the protons of the equatorial C_{16}-carbomethoxyl group.



XXa XXb



The D/E ring juncture stereochemistry of the heteroyohimbine bases could be distinguished by Wenkert *et al.*[127]. They showed that the spin-spin coupling constant associated with the interaction of C_{19}- and C_{20}-protons remains virtually unaltered with D/E-*trans* but varies with the D/E-*cis* isomers. Thus, the one-proton down field octet ($\delta = 4{\cdot}36$-$4{\cdot}44$) characteristic of C_{19}-H coupling with C_{20}-H and the methyl group shows J_{HH} to be 2·7 and 1·8 cps for *normal* (XXI) and *pseudo* (XXII) respectively, while the respective values for *allo* (XXIII) and *epi-allo* (XXIV) are 10·3 and 5·8 cps.

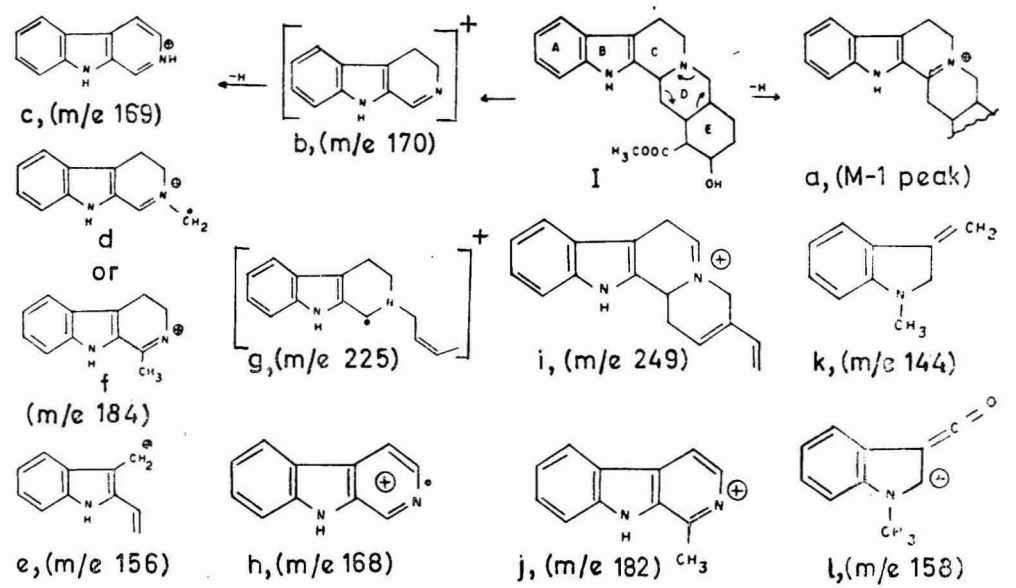
Shamma and Moss[129] observed that the chemical shifts of the $^{+}N\text{-}CH_3$ protons of the corresponding methyl salts of *allo* and *epi-allo* compounds could distinguish the nature of fusion of C/D ring system. The $^{+}N\text{-}CH_3$ protons show peaks at lower fields ($\delta = 3{\cdot}49$-$3{\cdot}50$) in methiodides with *cis*-fused C/D rings than in the *trans*-fused ($\delta = 3{\cdot}31$-$3{\cdot}43$) analogues. This observation is difficult to accept without reservation because of the complexity of the molecule where Katritzky's observation based on simple system may not hold. The stereochemical assignment of the C_{19}-methyl group by the same authors from the chemical shifts of the C_{19}-methyl doublets in the NMR spectra on methiodide formation is not well apparent.

In any case, the study of NMR spectra is expected to be useful for the assignment either of structures[130] or conformations of closely related compounds.

Mass Spectra

It is only in the beginning of 1960's that mass spectrometry has been applied in the field of alkaloids[131-133]. Therefore, like NMR, this tool did not actually help elucidate the structures of *Rauwolfia* alkaloids, but detailed studies revealed some characteristic fragmentation patterns.

The most characteristic peak, common to the major types, viz. yohimbine, heteroyohimbine and sarpagine, appears to be an intensely strong M-1 peak arising out of the loss of a hydrogen atom at C_3 or C_6 depending on the ease of stabilization by conjugation with the indole system. Both yohimbine and heteroyohimbine types exhibit peaks at *m/e* 156, 169, 170 and 184, all incorporating indole moiety. While no stereochemical assignment to the yohimbine isomers is possible because of their very close mass spectral pattern, the relative intensities of these peaks permit the differentiation of the stereochemistry at the D/E ring junctions of the heteroyohimbine bases. An additional ion peak at *m/e* 225 (species *g*) with enhanced intensities of those at *m/e* 156 and 184 distinguishes heteroyohimbine from the yohimbine series. The general mechanism[132] involves a retro-Diels-Alder fragmentation of ring C followed by the homolytic fission of the allylically activated bonds. Of course, a concerted process starting from the allylic bond at C_3-C_{14} in ring D also may account for some fragments, e.g. species *b-d*. In sarpagine type, while *m/e* 169 must be identical with the carbolinium cation (*c*) found in yohimbine type, *m/e* 168 (*h*) could be assigned to β-carboline ion itself[134]. Further, the compounds with ethylidene function at C_{20} such as sarpagine (Xb) can be distinguished from the corresponding dihydro compounds by an intense



peak at *m/e* 249 (*i*) and by a less intense peak at *m/e* 182 (*j*) corresponding to *m/e* 184 (*d*) in yohimbine type[135].

In dihydroindole series, the mass spectra of ajmaline[136], ajmalidine, vomalidine[137] and tetraphyllicine[138] have been studied. It appears that the carbolinium cation (*c*), with due consideration to the substituents in the indole moiety, is the common fragment of all the β-carboline derivatives. Thus, the ion peaks at *m/e* 182 and 183 in ajmaline type corresponds to those at *m/e* 168 and 169 in yohimbine type. The assignment to other peaks are certainly not unambiguous[132]. It has been observed by Biemann *et al.*[137] that the difference in substitution and/or stereochemistry at the alicyclic ring system sometimes radically changes the fragmentation pattern. For instance, in ajmalidine the characteristic peaks for the β-carbolinium cations are of much lower intensity than those of ajmaline, and the most intense peaks appear at *m/e* 144 (*k*) and *m/e* 158 (*l*). The latter fragment which must contain the C_{17}-oxygen function along with the indole moiety is considered to be quite diagnostic of ajmaline ring system. Epimerization at C_2 has been noted to have profound effect on the fragmentation pattern[138].

It is at least safe to conclude that mass spectrometry not only provides important clues to the skeletal structures but also helps stereochemical assignments in certain cases.

Other Physico-chemical Methods

Molecular Rotation and Optical Rotatory Dispersion

The generalized method of molecular rotation differences and the optical rotatory dispersion studies which proved to be so useful in the steroid field have been extended with advantage by Klyne[139] and Djerassi *et al.*[140] in the stereochemical assignment of the asymmetric centres of the D/E rings of yohimbine. Recently, Finch *et al.*[141] reported that for heteroyohimbine bases the sign and magnitude of the Cotton effect at 235-255 mμ is dependent on the ring juncture stereochemistry, irrespective of the orientation of C_{19}-methyl group. Ring A unsubstituted compound with 3α, 20α configuration shows negative Cotton effect with high amplitude (−1100), while all other possible combinations (the configuration of the C_{15}-H being α and the same for all the known *Rauwolfia* alkaloids) exhibit positive Cotton effect, the highest amplitude (+1100) being recorded for the 3β, 20β compound. Substituent in ring A definitely influences the ORD extrema, but the extent to which the amplitudes are affected remains to be determined.

Kinetic Studies

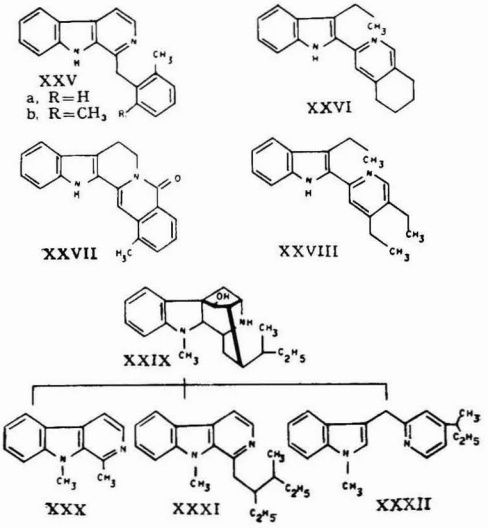
Studies on the pseudo-first order rates of methiodide formation proved to be of particular importance. This rate which should be fast for those possessing the *normal* (XXI) configuration and very slow for the *allo* (XXIII) group of alkaloids corroborated the known stereochemistry of yohimbine bases. However, the order of the rate constants necessitated the reversal of the previously assigned stereochemistry at the D/E ring junction of the heteroyohimbine alkaloids. The revised stereochemistry currently accepted was supported by the pK_a values. As expected, the less hindered *trans* compounds were found to be more basic than the *cis*-isomers[122] in 66 per cent dimethylformamide in water.

General Approaches to Structure and Stereochemistry

With the advent of modern physico-chemical methods, the task of structure elucidations of natural products has become comparatively simple in recent years. The modern chemists have to bother less about the detailed classical approaches that remarkably established the structure and gross stereochemistry of *Rauwolfia* alkaloids[3,4,18,21,142-146]. Yet some of them still retain their usefulness.

Selenium dehydrogenation[3,145] alone has proved to be extremely valuable in determining the basic skeletal structures. Yohimbine and its congeners yield three characteristic dehydrogenation products, viz. yobyrine (XXVa), tetrabyrine (XXVI) and ketoyobyrine (XXVII). The remarkable formation of ketoyobyrine involving aromatization of ring E, cleavage of the C_{21}-N_4 linkage, rotation of ring E through 180° about the C_{14}-C_{15} axis followed by lactam formation and subsequent dehydrogenation not only settles the pentacyclic structure of yohimbine isomers but also provides indirect evidence of the location of the carbomethoxyl group at C_{16}. The latter is definitely proved[147,148] by the selenium dehydrogenation of the $LiAlH_4$ reduction product of the yohimbine bases to yield methylyobyrine (XXVb). The heteroyohimbine bases, on the other hand, provide alstyrene (XXVIII), quite characteristic and diagnostic of this class of compounds. The methoxy substituent(s) in ring A is generally retained in this process.

Woodward[149] has shown that Pd/C dehydrogenation of deoxydihydro-ajmaline (XXIX), a degradation product of ajmaline, affords three characteristic

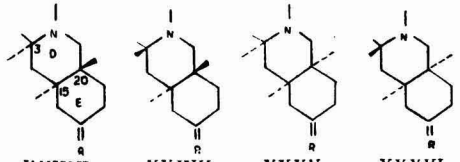


products (XXX–XXXII) and N_b common to two six-membered rings is retained in one or the other in this drastic cleavage.

Saponification and re-esterification establish the presence and conformation of the carbomethoxyl function[143]. All the known yohimbine isomers regenerate the original compound except corynanthine which yields yohimbine under the same conditions. Clearly, the carbomethoxyl group must have the less stable axial conformation in the latter while in all others it is equatorial.

In 18-hydroxy-yohimbine type, the presence and the equatorial orientation of the ester groups at C_{17} and C_{18} (no axial epimer yet been encountered in nature) have analogously been established by alkaline hydrolysis and regeneration of the original ester-alkaloid. The facile γ-lactonization of reserpic acid and N_b quaternization of the C_{16}- and C_{18}-tosyloxy derivatives of the appropriate alcohols support the equatorial orientation of the functions at C_{16} and C_{18} and, in addition, requires *cis*-fused D/E ring system[3].

Oppenauer oxidation and Wolff-Kishner (Huang-Minlon) reduction have been extensively used. In case of yohimbine isomers, oxidation of the original base or the corresponding acid affords a carbomethoxyl free ketone (XXXIIIa) which must arise via an intermediate β-keto acid. This process secures the secondary nature and C_{17} position of the alcoholic function the conformation of which is determined either by *trans*-elimination, equilibration or stereospecific reduction of the ketone. Oppenauer oxidation of deoxyajmaline to a five-membered ring ketone provided valuable evidence[149] against the structure of ajmaline earlier proposed by Anet *et al.*[150] with a tertiary hydroxyl group in a four-membered caged ring.



XXXIII XXXIV XXXV XXXVI

a, R = O; b, R = H_2

Wolff-Kishner reduction of ajmaline isomers mainly furnishes evidence of the presence of carbinolamine system and in yohimbine series it helps elucidate the ring juncture stereochemistry while in heteroyohimbines this method along with Oppenauer oxidation has been applied for correlation. In yohimbines, the asymmetric centres in both the ketone and the deoxy compound are practically reduced to three neglecting the possible isomerism due to the lone pair of electrons at N_4, since the *trans*-configuration of the C/D ring is definitely preferred. This aspect has not been fully investigated for the yohimbine type, but in heteroyohimbine bases it has been studied by physical methods. The stereochemistry at the other ring junctures has already been dealt with[3,143] exhaustively and, therefore, only the salient features will be discussed very briefly.

Of the three asymmetric centres at C_3, C_{15} and C_{20}, the configuration of C_{15}-H is α and the same for all the *Rauwolfia* alkaloids[151,152]. Four possible configurations, viz. *normal* (*syn-anti*, XXXIII), *pseudo* (*anti-anti*, XXXIV), *allo* (*syn-syn*, XXXV) and *epi-allo* (*anti-syn*, XXXVI), are represented by the respective ketones of yohimbine, Ψ-yohimbine, *allo*-yohimbine and 3-*epi*-α-yohimbine. Wolff-Kishner method affords either yohimbane or *allo*-yohimbane having *normal* (XXXIVb) or *allo* (XXXVIb) configuration depending on the *trans* or *cis* D/E ring fusion of the ketone, the C_3-H of which epimerizes to the more stable α-configuration under the highly alkaline condition of reduction. Acid-induced epimerization has also been realized. Oxidation of ring C with lead tetraacetate, mercuric acetate or palladium and maleic acid followed by reintroduction of the C_3-centre with stereospecific reducing agents also serves to distinguish the absolute stereochemistry particularly at this centre of both yohimbine and heteroyohimbine alkaloids. Hydrogenation or $NaBH_4$ reduction of the tetradehydro or 3-dehydro compounds leads exclusively to *normal* or predominantly to *allo* products depending on the *trans* or *cis* nature of the D/E ring system while the C_3-H β(*e*)-epimer is obtained when zinc and acid is used to reduce the Δ^3-compound[143,144]. Mercuric acetate oxidation appears to be diagnostic[153] of the α- or β-configuration of the C_3-H as also its axial or equatorial nature in *normal* and *pseudo* compounds with unambiguous conformation, if not in a *cis*-fused D/E ring system. The relative rates of palladium and maleic acid dehydrogenation can differentiate between *pseudo* and *epi-allo* in heteroyohimbine bases[123,124].

Lead tetraacetate oxidation of 21-deoxyajmaline leading to an indole-aldehyde affords one important evidence[149] to the structure of ajmaline. Moreover, the correlation of this aldehyde, deoxyajmalal-A, with corynantheidane definitely establishes the stereochemistry of the hexacyclic system and C-ethyl in ajmaline. The stereochemistry of other alkaloids in this group is mainly based on the correlation with either the deoxyajmaline or the derived aldehyde[21,144].

The formation of 2,4-dinitrophenylhydrazone depending on the hydrolytic cleavage of the dihydropyran structure of ring E heterocyclic compounds has been found to be characteristic of those (e.g. alstonine, VII) with *cis*-fused D/E rings only. This criterion has been taken advantage of[154] in distinguishing them from their *trans* relatives (e.g. serpentine, VIII). The anhydronium bases (VII and VIII) are interrelated to tetrahydroalstonine (VIa) and ajmalicine (Va) by hydrogenation, or conversely, by lead tetraacetate oxidation.

The absolute configuration of ajmalicine type at C_3, C_{15} and C_{20} has been established by its correlation with the 17,18-seco-yohimbane, dihydrocorynantheane[151], through a series of reactions involving saponification, decarboxylation, Wolff-Kishner reduction, Oppenauer oxidation followed by Wolff-Kishner reduction. Two types of ring junctures, viz. *trans* and *cis*, of the D/E ring system of yohimbine type have also been correlated[151] through the preparation of two enantiomorphic

16-yohimbones from the *apo* derivatives of yohimbine and 3-*epi*-α-yohimbine by Schmidt reaction.

All the 18-hydroxy-yohimbine alkaloids are known to have *cis* fusion at D/E ring junction. All of them including 19-dehydro analogues have C_3-H β-oriented except isoreserpine (IIIh) which is not yet recognized as a natural product[20]. The assignment of their stereochemistry is mainly based on the correlation of the 18-deoxy compound without ring A substituent (e.g. deserpidine, IIIc) with α-yohimbine or its epimer[3].

Much of the chemistry of *Rauwolfia* alkaloids is concerned mostly with the stereochemical problems. A combination of physical methods already discussed, conformational analysis and biogenetic considerations has played important roles in elucidating the absolute stereochemistry of this class of alkaloids. The researches in this field also stimulated stereospecific synthesis of complex alkaloids like reserpine[12], yohimbine[155] and total synthesis of ajmalicine[156].

It is pertinent to mention that attempts were made[157,158] from this laboratory to correlate the stereochemistry of yohimbine and its congeners with the pharmacological activities. The absolute configuration of the C_{19}-methyl group in heteroyohimbine bases predicted[158] on the assumed correctness of the then knowledge of stereochemistry at other centres obviously cannot be valid with the subsequent reversal[122] of configurations at the D/E ring junctions. However, we believe, a re-examination of this approach may not prove to be unrewarding. Nevertheless, the dependence of the pharmacological activities on many factors including species variation is the main difficulty inherent in such a study.

Biogenesis

The earlier concept[149,159-161] of biogenesis of indole alkaloids including those from *Rauwolfia* has been the subject of serious rethinking in recent years in the light of radioisotopic tracer studies. While the derivation of the β-carboline moiety from tryptophan or its equivalent appears to be well authenticated[162,163], the origin of the non-tryptophan derived portion is still not properly understood. Four hypotheses have so far been advanced involving (i) 3,4-dihydroxyphenylalanine (Woodward[149]), (ii) prephenic acid (Wenkert[151,164]), (iii) acetic acid-malonic acid (Leete[165,166]) and (iv) cyclopentanoid monoterpene skeleton derivable from mevalonic acid (Thomas[167] and Wenkert[168]). The findings[169-171] that a one-carbon fragment is not involved in the biogenesis eliminate the first three possibilities. Thus, the current indications supported[172] by feeding experiments with sodium (±)-[2-C^{14}]-mevalonate are in favour of the mevalonoid origin of the C_{9-10} unit of this class of compounds.

In retrospect, the researches on *Rauwolfia* alkaloids proved to be extremely valuable and rewarding not only because the enriched knowledge in this field sparked off renewed interest in other indole alkaloids and helped elucidate novel structural patterns of considerable biogenetic significance but also because they provide yet another good example of the importance of work on natural products both for research and industry.

Summary

The general physico-chemical characteristics, important structural features, general approach to the determination of structure and stereochemistry, and biogenesis of *Rauwolfia* alkaloids have been reviewed. An up-to-date classified list of alkaloids with their sources has also been included.

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References

1. Plumier, P. C., *Nova Plantarum Americanarum Genera*, 1703, 19.
2. Chatterjee, A., cited in *Fortschr. Chem. org. NatStoffe*, Vol. 10, edited by L. Zechmeister (Springer-Verlag, Vienna), 1953, 390.
3. Chatterjee, A., Pakrashi, S. C. & Werner, G., cited in *Fortschr. Chem. org. NatStoffe*, Vol. 13, edited by L. Zechmeister (Springer-Verlag, Vienna), 1956, 346.
4. Woodson (Jr), R. E., Youngken, H. W., Schlittler, E. & Schneider, J. A., *Rauwolfia* (Little, Brown & Co., Boston), 1957.
5. Siddiqui, S. & Siddiqui, R. H., *J. Indian chem. Soc.*, **8** (1931), 667.
6. Siddiqui, S. & Siddiqui, R. H., *J. Indian chem. Soc.*, **9** (1932), 539.
7. Siddiqui, S. & Siddiqui, R. H., *J. Indian chem. Soc.*, **12** (1935), 37.
8. Siddiqui, S., *J. Indian chem. Soc.*, **16** (1939), 421.
9. Chatterjee (*née* Mookerjee), A., *J. Indian chem. Soc.*, **18** (1941), 33.
10. Chatterjee, A. & Pakrashi, S., *Naturwissenschaften*, **41** (1954), 215.
11. Mueller, J. M., Schlittler, E. & Bein, H. J., *Experientia*, **8** (1952), 338.
12. Woodward, R. B., Bader, F. E., Bickel, H., Frey, A. J. & Kierstead, R. W., *J. Am. chem. Soc.*, **78** (1956), 2023, 2657.
13. Lucas, R. A., cited in *Progress in medicinal chemistry*, Vol. 3, edited by G. P. Ellis & G. V. West (Butterworths Scientific Publications, London), 1963, 146.
14. Saxton, J. E., *Q. Rev. chem. Soc.*, **10** (1956), 128.
15. Hofmann, A., *Planta med.*, **56** (1957), 145.
16. Rauwolfia alkaloids in *Research today* (Eli Lilly & Co., Indianapolis), 1958.
17. Chatterjee, A. & Ray, A. B., *J. scient. ind. Res.*, **21A** (1962), 515.
18. Saxton, J. E., cited in *The alkaloids*, Vol. 7, edited by R. H. F. Manske (Academic Press Inc., New York), 1960, 62.
19. Schlittler, E., Druey, J. & Marxer, A., cited in *Progress in drug research*, Vol. 4, edited by E. Jucker (Birkhauser, Basel), 1962, 295.
20. Schlittler, E., cited in *The alkaloids*, Vol. 8, edited by R. H. F. Manske (Academic Press Inc., New York), 1965, 287.
21. Taylor, W. I., cited in *The alkaloids*, Vol. 8, edited by R. H. F. Manske (Academic Press Inc., New York), 1965, 785.
22. Bhattacharji, S., Dhar, M. M. & Dhar, M. L., *J. scient. ind. Res.*, **15B** (1956), 506; **16B** (1957), 97.
23. Stoll, A. & Hofmann, A., *Society of Biological Chemists (India) silver jubilee souvenir*, 1955, 248; *J. Am. chem. Soc.*, **77** (1955), 820.
24. Hofmann, A., *Helv. chim. Acta*, **37** (1954), 314.
25. Poisson, J., Le Hir, A., Goutarel, R. & Janot, M. M., *C.r. hebd. Séanc. Acad. Sci., Paris*, **239** (1954), 302.
26. Bernal, R. M., Villegas-Castillo, A. & Espejo, O. P., *Experientia*, **16** (1960), 353.
27. Haack, E., Popelak, A., Spingler, H. & Kaiser, F., *Naturwissenschaften*, **41** (1954), 479.

28. ADITYACHAUDHURY, N. & CHATTERJEE, A., *J. scient. ind. Res.*, **18B** (1959), 130.
29. MUELLER, J. M., *Experientia*, **13** (1957), 479.
30. BADER, F. E., DICKEL, D. F. & SCHLITTLER, E., *J. Am. chem. Soc.*, **76** (1954), 1695.
31. CHATTERJEE, A., *Proceedings of the symposium of phytochemistry, Kuala Lumpur*, 1957, 142.
32. ISHIDATE, M., OKADA, M. & SAITO, K., *Pharm. Bull. Tokyo*, **3** (1955), 319.
33. HAACK, E., POPELAK, A. & SPINGLER, H., *Naturwissenschaften*, **43** (1956), 328.
34. HOCHSTEIN, F. A., *J. org. Chem.*, **21** (1956), 1516.
35. HOCHSTEIN, F. A., MURAI, K. & BOEGEMANN, W. H., *J. Am. chem. Soc.*, **77** (1955), 3551.
36. VERGARA, B. U., *J. Am. chem. Soc.*, **77** (1955), 1864; *An. Soc. Biol. Bogotá*, **6** (1955), 277.
37. HOFMANN, A., *Helv. chim. Acta*, **38** (1955), 536.
38. BADER, F. E., DICKEL, D. F., LUCAS, R. A. & SCHLITTLER, E., *Experientia*, **10** (1954), 298.
39. STOLL, A. & HOFMANN, A., *J. Am. chem. Soc.*, **77** (1955), 820.
40. DJERASSI, C., FISHMAN, J., GORMAN, M., KUTNEY, J. P. & PAKRASHI, S. C., *J. Am. chem. Soc.*, **79** (1957), 1217.
41. SCHLITTLER, E., ULSHAFER, P. R., PANDOW, M. L., HUNT, R. M. & DORFMAN, L., *Experientia*, **11** (1955), 64.
42. KLOHS, M. W., KELLER, F., WILLIAMS, R. E. & KUSSEROW, G. W., *J. Am. chem. Soc.*, **77** (1955), 4084.
43. NEUSS, N., BOAZ, H. E. & FORBES, J. W., *J. Am. chem. Soc.*, **77** (1955), 4087.
44. HARRISSON, J. W. E., PACKMAN, E. W., SMITH, E., HOSANSKY, N. & SALKIN, R., *J. Am. pharm. Ass. Scient. Edn*, **44** (1965), 688.
45. KORZUN, B. P., ST ANDRÉ, A. F. & ULSHAFER, P. R., *J. Am. pharm. Ass. Scient. Edn*, **46** (1957), 720.
46. MUELLER, J., *Swiss Pat. No.* 361,814 (1962); *Chem. Abstr.*, **59** (1963), 11591.
47. HOSANSKY, N. & SMITH, E., *J. Am. pharm. Ass. Scient. Edn*, **44** (1955), 639.
48. CIBA Ltd, *Br. Pat. No.* 833,149; *Chem. Abstr.*, **54** (1960), 21666.
49. VAN TAMELEN, E. E. & TAYLOR, C. W., *J. Am. chem. Soc.*, **79** (1957), 5256.
50. ULSHAFER, P. R., TAYLOR, W. I. & NUGENT, R. H., *C.r. hebd. Séanc. Acad. Sci., Paris*, **244** (1957), 2989.
51. POPELAK, A., HAACK, E., LETTENBAUER, G. & SPINGLER, H., *Naturwissenschaften*, **48** (1961), 73.
52. HOFMANN, A., *Helv. chim. Acta*, **37** (1954), 849.
53. KLOHS, M. W., KELLER, F., WILLIAMS, R. E. & KUSSEROW, G. W., *Chemy Ind.*, (1956), 187.
54. SMITH, E., JARET, R. S., SHAMMA, M. & SHINE, R. J., *J. Am. chem. Soc.*, **86** (1964), 2083.
55. ULSHAFER, P. R., PANDOW, M. L. & NUGENT, R. H., *J. org. Chem.*, **21** (1956), 923.
56. BOSE, S., TALAPATRA, S. K. & CHATTERJEE, A., *J. Indian chem. Soc.*, **33** (1956), 379.
57. KECK, J., *Naturwissenschaften*, **42** (1955), 391.
58. TALAPATRA, S. K., *J. scient. ind. Res.*, **21B** (1962), 198.
59. SHAVEL, J., KANE, G. & KING, J. A., *American Chemical Society 126th meeting, New York*, 1954, 25N; RAO, D. S. & RAO, S. B., *J. Am. pharm. Ass. Scient. Edn*, **44** (1955), 253.
60. SALKIN, R., HOSANSKY, N. & JARET, R., *J. pharm. Sci.*, **50** (1961), 1038.
61. PAKRASHI, S. C., DJERASSI, C., WASICKY, R. & NEUSS, N., *J. Am. chem. Soc.*, **77** (1955), 6687.
62. NEUSS, N., BOAZ, H. E. & FORBES, J. W., *J. Am. chem. Soc.*, **76** (1954), 3234.
63. KLOHS, M. W., DRAPER, M. D., KELLER, F., MALESH, W. & PETRACEK, F. J., *J. Am. chem. Soc.*, **76** (1954), 1332.
64. KLOHS, M. W., DRAPER, M. D. & KELLER, F., *J. Am. chem. Soc.*, **76** (1954), 2843; *see* also HAACK, E., POPELAK, A., SPINGLER, H. & KAISER, F., *Naturwissenschaften*, **41** (1954), 214; **42** (1955), 47.
65. ARTHUR, H. R., *Chemy Ind.*, (1956), 85.
66. YAMAGUCHI, K. & SHOJI, H., *Bull. natn. hyg. Lab., Tokyo*, **76** (1958), 99; *Chem. Abstr.*, **53** (1959), 17419.
67. STOLL, A., HOFMANN, A. & BRUNNER, R., *Helv. chim. Acta*, **38** (1955), 270.
68. IACOBUCCI, G. & DEULOFEU, V., *J. org. Chem.*, **22** (1957), 94; *An. Asoc. quim. Argent.*, **46** (1958), 143; *Chem. Abstr.*, **53** (1959), 3595.
69. KIDD, D. A. A., *J. chem. Soc.*, (1958), 2432.
70. ATAL, C. K., *J. Am. pharm. Ass. Scient. Edn*, **48** (1959), 37.
71. KIANG, A. K. & WAN, A. S. C., *J. chem. Soc.*, (1960), 1394.
72. POISSON, J. & GOUTAREL, R., *Bull. Soc. chim. Fr.*, (1956), 1703.
73. GOUTAREL, R., GUT, M. & PARELLO, J., *C.r. hebd. Séanc. Acad. Sci., Paris*, **253** (1961), 2589.
74. PERNET, R., PHILIPPE, J. & COMBES, G., *Annls pharm. fr.*, **20** (1962), 527.
75. RAO, D. S. & RAO, S. B., *Indian J. pharm.*, **18** (1956), 202.
76. SCHLITTLER, E., SANER, H. & MUELLER, J. M., *Experientia*, **10** (1954), 133; *see* also WEISENBORN, F. L., MOORE, M. & DIASSI, P. A., *Chemy Ind.*, (1954), 375.
77. FINCH, N., ULSHAFER, P. R. & TAYLOR, W. I., *Experientia*, **19** (1963), 296.
78. GORMAN, M., NEUSS, N., DJERASSI, C., KUTNEY, J. P. & SCHEUER, P. J., *Tetrahedron*, **1** (1957), 328.
79. DJERASSI, C. & FISHMAN, J., *Chemy Ind.*, (1955), 627.
80. SCHLITTLER, E., SCHWARZ, H. & BADER, F., *Helv. chim. Acta*, **35** (1952), 271.
81. SEBA, R. A., CAMPOS, J. S. & KUHLMANN, J. G., *Bolm. Inst. Vital Braz.*, **5** (1954), 175; *Chem. Abstr.*, **49** (1955), 14270.
82. JANOT, M. M., GOUTAREL, R. & LE HIR, A., *C.r. hebd. Séanc. Acad. Sci., Paris*, **238** (1954), 720.
83. DJERASSI, C., GORMAN, M., NUSSBAUM, A. L. & REYNOSO, J., *J. Am. chem. Soc.*, **76** (1954), 4463.
84. PARIS, R., *Annls pharm. fr.*, **1** (1943), 138.
85. PILLAY P. P., RAO, D. S. & RAO, S. B., *J. scient. ind. Res.*, **19B** (1960), 135.
86. TALAPATRA, S. K. & CHATTERJEE, A., *Sci. & Cult.*, **22** (1957), 692.
87. BODENDORF, K. & EDER, H., *Chem. Ber.*, **87** (1954), 818.
88. STOLL, A. & HOFMANN, A., *Helv. chim. Acta*, **36** (1953), 1143.
89. ADITYACHAUDHURY, N. & CHATTERJEE, A., *J. scient. ind. Res.*, **18B** (1959), 398.
90. SCHEUER, P. J., CHANG, M. Y. & FUKAMI, H., *J. org. Chem.*, **28** (1963), 2641.
91. COURT, W. E., EVANS, W. C. & TREASE, G. E., *J. Pharm. Pharmac.*, **10** (1958), 380.
92. SCHULER, B. O. G. & WARREN, F. L., *J. chem. Soc.*, (1956), 215.
93. CHATTERJEE, A. & TALAPATRA, S., *Naturwissenschaften*, **42** (1955), 182.
94. MONSEUR, X., *J. Pharm. Belg.*, **12** (1957), 39.
95. ROLAND, M., *J. Pharm. Belg.*, **14** (1959), 347.
96. POISSON, J., ULSHAFER, P. R., PASZEK, L. E. & TAYLOR, W. I., *Bull. Soc. chim. Fr.*, (1964), 2683.
97. POUSSET, J. L. & POISSON, J., *Annls pharm. fr.*, **23** (1965), 733.
98. POISSON, J., GOUTAREL, R. & JANOT, M. M., *C.r. hebd. Séanc. Acad. Sci., Paris*, **241** (1955), 1840.
99. CHATTERJEE, A. & BOSE, S., *Sci. & Cult.*, **17** (1951), 139.
100. BOSE, S., *Naturwissenschaften*, **42** (1955), 71.
101. PATEL, M. B., POISSON, J., POUSSET, J. L. & ROWSON, J. M., *J. Pharm. Pharmacol.*, **17** (1965), 323.
102. HOFMANN, A. & FREY, A. J., *Helv. chim. Acta*, **40** (1957), 1866.
103. MUELLER, J. M., cited in *Experientia*, **19** (1963), 296.
104. KHAN, N. H., KHAN, M. A. & SIDDIQUI, S., *Pakist. J. scient. ind. Res.*, **8** (1965), 23.
105. ULSHAFER, P. R., BARTLETT, M. F., DORFMAN, L., GILLEN, M. A., SCHLITTLER, E. & WENKERT, E., *Tetrahedron Lett.*, (No. 11), (1961), 363.
106. TAYLOR, W. I., FREY, A. J. & HOFMANN, A., *Helv. chim. Acta*, **45** (1962), 611.
107. POUSSET, J. L. & POISSON, J., *C.r. hebd. Séanc. Acad. Sci., Paris*, **259** (1964), 597.
108. GOMEZ, L., DA SILVA, P. & GARRIA, P., *J. Philipp. pharm. Ass.*, **44** (1957), 127.
109. RAKSHIT, B., *Indian pharmst*, **10** (1954), 84.

110. NEUSS, N. (Ed.), *Lilly collection of physical data of indole and dihydroindole alkaloids* (Lilly Research Laboratories, Indianapolis, Indiana), 1960 *et seq.*
111. KOEPFLI, J. B., *J. Am. chem. Soc.*, **54** (1932), 2412.
112. LIU, C. C., LO, J. Y. & SHI, LI, *K'o Hsueh T'ung Pao*, (1958), 52; *Chem. Abstr.*, **55** (1961), 24802.
113. SCHLITTLER, E. & FURLENMEIER, A., *Helv. chim. Acta*, **36** (1953), 996.
114. KLOHS, M. W., DRAPER, M. D., KELLER, F. & MALESH, W., *Chemy Ind.*, (1954), 1264.
115. KIDD, D. A. A., *Chemy Ind.*, (1955), 1481.
116. HESSE, M., *Indolalkaloide in Tabellen* (Springer-Verlag, Berlin), 1964.
117. SANGSTER, A. W. & STUART, K. L., *Chem. Rev.*, **65** (1965), 69.
118. CHAMBERS, J. R., OPENSHAW, H. T. & SMITH, G. F., *J. chem. Soc.*, (1954), 1115.
119. ROBINSON, B. & SPITTELER, G., *Chemy Ind.*, (1964), 459.
120. WITKOP, B. & PATRICK, J. B., *J. Am. chem. Soc.*, **73** (1951), 2188.
121. NEUSS, N. & BOAZ, H. E., *J. org. Chem.*, **22** (1957), 1001.
122. SHAMMA, M. & MOSS, J. B., *J. Am. chem. Soc.*, **83** (1961), 5038.
123. WENKERT, E. & ROYCHAUDHURI, D. K., *J. Am. chem. Soc.*, **78** (1956), 6417.
124. WENKERT, E. & ROYCHAUDHURI, D. K., *J. Am. chem. Soc.*, **80** (1958), 1613.
125. ALBRIGHT, J. D., MITSCHER, L. A. & GOLDMAN, L., *J. org. Chem.*, **28** (1963), 38.
126. ROSEN, W. E. & SHOOLERY, J. N., *J. Am. chem. Soc.*, **83** (1961), 4816.
127. WENKERT, E., WICKBERG, B. & LEICHT, C. L., *J. Am. chem. Soc.*, **83** (1961), 5037.
128. ROSEN, W. E. & SHEPPARD, H., *J. Am. chem. Soc.*, **83** (1961), 4240.
129. SHAMMA, M. & MOSS, J. B., *J. Am. chem. Soc.*, **84** (1962), 1739.
130. CHATTERJEE, A. & BOSE, S., *J. Indian chem. Soc.*, **38** (1961), 403.
131. BIEMANN, K., *Mass spectrometry* (McGraw-Hill Book Co. Inc., New York), 1962.
132. BUDZIKIEWICZ, H., DJERASSI, C. & WILLIAMS, D. H., *Structure elucidation of natural products by mass spectrometry*, Vol. I (Holden-Day Inc., San Francisco), 1964.
133. PAKRASHI, S. C., *Proc. natn. Acad. Sci., India*, **35** (Pt 4) (1965), 465.
134. BIEMANN, K., *J. Am. chem. Soc.*, **83** (1961), 4801.
135. ANTONACCIO, L. D., PEREIRA, N. A., GILBERT, B., VORBRÜGGEN, H., BUDZIKIEWICZ, H., WILSON, J. N. & DJERASSI, C., *J. Am. chem. Soc.*, **84** (1962), 2161.
136. SPITELLER, G. & SPITELLER-FRIEDMANN, M., *Tetrahedron Lett.*, (No. 3), (1963), 147.
137. BIEMANN, K., BOMMER, P., BURLINGAME, A. L. & MCMURRAY, W. J., *Tetrahedron Lett.*, (No. 28), (1963), 1969.
138. GORMAN, M., BURLINGAME, A. L. & BIEMANN, K., *Tetrahedron Lett.*, (No. 1), (1963), 39.
139. KLYNE, W., *Chemy Ind.*, (1953), 1032.
140. DJERASSI, C., RINIKER, R. & RINIKER, B., *J. Am. chem. Soc.*, **78** (1956), 6362.
141. FINCH, N., TAYLOR, W. I., EMERSON, T. R., KLYNE, W. & SWAN, R. J., *Tetrahedron*, **22** (1966), 1327.
142. MARION, L., *The alkaloids*, Vol. 2, edited by R. H. F. Manske & H. L. Holmes (Academic Press Inc., New York), 1952, 408.
143. PAKRASHI, S. C., *Ann. Biochem. exp. Med.*, **20** (1960), 77.
144. PAKRASHI, S. C., *J. Indian chem. Soc.*, **38** (1961), 587.
145. BOEKELHEIDE, V. & PRELOG, V., *Progress in organic chemistry*, Vol. 3, edited by J. W. Cook (Butterworths Scientific Publications, London), 1955, 218, for leading references.
146. MANSKE, R. H. F., *The alkaloids*, Vol. 8, edited by R. H. F. Manske (Academic Press Inc., New York), 1965, 693.
147. CHATTERJEE, A. & PAKRASHI, S. C., *J. Indian chem. Soc.*, **38** (1959), 685.
148. KARRER, P., SCHWYZER, R., FLAM, A. & SAEMANN, R., *Helv. chim. Acta*, **35** (1952), 865.
149. WOODWARD, R. B., *Angew. Chem.*, **68** (1956), 13.
150. ANET, F. A. L., CHAKRAVARTI (*née* MUKHERJEE), D., ROBINSON, R. & SCHLITTLER, E., *J. chem. Soc.*, (1954), 1242.
151. WENKERT, E. & BRINGI, N. V., *J. Am. chem. Soc.*, **81** (1959), 1474.
152. BOSE, A. K., CHATTERJEE, B. G. & SITARAM IYER, R., *Indian J. Pharm.*, **18** (1956), 185.
153. WEISENBORN, F. L. & DIASSI, P. A., *J. Am. chem. Soc.*, **78** (1956), 2022.
154. CHATTERJEE, A. & TALAPATRA, S. K., *Sci. & Cult.*, **20** (1955), 568.
155. VAN TAMELEN, E. E., SHAMMA, M., BURGSTAHLER, A. W., WOLINSKY, J., TAMM, R. & ALDRICH, P. E., *J. Am. chem. Soc.*, **80** (1958), 5006.
156. VAN TAMELEN, E. E. & PLACEWAY, C., *J. Am. chem. Soc.*, **83** (1961), 2594.
157. PAKRASHI, S. C., *Ann. Biochem. exp. Med.*, **20** (1960), 309.
158. PAKRASHI, S. C., *Ann. Biochem. exp. Med.*, **21** (1961), 367.
159. ROBINSON, R., *The structural relations of natural products* (Oxford University Press, Oxford), 1955.
160. LEETE, E., *Elucidation of structure by physical and chemical methods*, Vol. 1, edited by A. Weissberger (Interscience Publishers Inc., New York), 1963, 413.
161. LEETE, E., *Biogenesis of natural compounds*, edited by P. Bernfeld (Pergamon Press Ltd, London), 1963, 739.
162. LEETE, E., AHMED, A. & KOMPIS, I., *J. Am. chem. Soc.*, **87** (1965), 4168.
163. LEETE, E., *J. Am. chem. Soc.*, **82** (1960), 6338.
164. WENKERT, E., *Experientia*, **15** (1959), 165.
165. LEETE, E., GHOSAL, S. & EDWARDS, P. N., *J. Am. chem. Soc.*, **84** (1962), 1068.
166. LEETE, E. & GHOSAL, S., *Tetrahedron Lett.*, (No. 25), (1962), 1179.
167. THOMAS, R., *Tetrahedron Lett.*, (No. 16), (1961), 544.
168. WENKERT, E., *J. Am. chem. Soc.*, **84** (1962), 98.
169. BATTERSBY, A. R., BINKS, R., LAWRIE, W., PARRY, G. V. & WEBSTER, B. R., *J. chem. Soc.*, (1965), 7459.
170. GOEGGEL, H. & ARIGONI, D., *Experientia*, **21** (1965), 369.
171. BARTON, D. H. R., KIRBY, G. W., PRAGER, R. H. & WILSON, E. M., *J. chem. Soc.*, (1965), 3990.
172. BATTERSBY, A. R., BROWN, R. T., KAPIL, R. S., PLUNKETT, A. O. & TAYLOR, J. B., *Chem. Commun., London*, (1966), 46.

Mechanism of Action of Intrauterine Contraceptive Devices*

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SCIENTIFIC interest in the *modus operandi* of the intrauterine contraceptive devices (IUCD) seems to be as old as their use as mechanical devices to prevent pregnancy. Haire[1] quotes Retschmensky as having observed an increase in *p*H of the uterus, the resultant high alkalinity preventing implantation. The oligodynamic action of silver of IUCDs made of this metal has been invoked in the prevention of pregnancy. Grafenburg[2] regards a 'hyperdecidual' condition of the endometrium provoked by the device as being responsible for preventing implantation. On the other hand, Carleton and Phelps[3] consider the anti-implantation effect of IUCDs to be largely due to physical coverage of the endometrial surface.

The revival of interest in IUCDs as a positive means for family planning and birth control has inevitably focused attention on their precise mode of action. This knowledge is urgently needed for future developments and refinements in this effective contraception technique, and to make it free from any unpleasant side effects.

Studies carried out to date on animals have revealed a marked species difference with respect to the points of impact of IUCDs in the reproductive mechanisms. Further, the devices may be of different composition and form. IUCDs in human and other primates are generally composed of polyethylene or stainless steel and are in shapes such as loops, coils, bows and rings. Devices in other animals of necessity have different shapes, since they have bicornuate uterus. In large domestic animals, such as sheep and cattle, IUCDs are spirals of polyethylene; in rodents they may be silk or nylon threads as well as spirals. Glass beads have also been used. The importance of these differences in composition, and even in strain (notably in rodents[4]), as well as the presence or absence of uterine distension which the devices may cause are, however, still imperfectly understood.

Accordingly, the status of the existing knowledge could be considered critically on the basis of the points in the reproductive mechanisms which have been shown to be influenced by IUCDs. Although for obvious reasons no attempts will be made to extrapolate knowledge derived from animal studies to the human, it may be interesting to examine any relevant and analogous clinical information on the mode of action of IUCDs.

Points of Impact of IUCDs

Ovulation

The only evidence that IUCDs may exert their contraceptive effect through inhibition of ovulation has been obtained in the Indian water buffalo[5] and, to a lesser extent, in cows[6]. An inhibitory effect of IUCD on corpus luteum function has been reported in guinea-pig, pig, sheep and cow[7-9]. This effect appears to be unilateral, i.e. on the corpora of the particular side bearing the IUCD[9]. However, in pigs an unilaterally placed IUCD inhibits corpus luteum development and implantation on both sides[10]. Contrary findings indicating an unilateral effect of IUCD on corpora in this species as in other animals have also been reported[11]. An increase in pituitary LH level has been noted in rabbits[12] and sheep[13] fitted with an IUCD. In rabbits, there is also a prolongation of several hours in the post-mating interval before ovulation in the presence of an IUCD[12]. However, the effect of an IUCD on steroid biosynthetic capacity of the corpus luteum is largely unknown. In rabbits, ovulation is apparently not disturbed[14,15].

In rhesus monkeys[16,17] and human[18-20] the ovulation process is unaffected by the IUCD. The cyclic pituitary-ovarian interplay is apparently undisturbed.

Sperm Transport and Capacitation

Interference with sperm transport has been recorded in sheep fitted with an IUCD[21]; sperms have been found to be absent or greatly reduced in number in both tubal washings, even though the IUCD was fitted in only one uterine horn. Also, sperms were found to be decapitated if injected into the IUCD-fitted horn of these animals. In fowl long-term presence of an IUCD disturbs sperm passage and survival[22]. It is interesting that the device also interferes with the deposition of shell and as a result shell-less eggs are produced.

In rodent species (rats, mice, hamsters, rabbits and ferrets), rhesus monkeys and human sperm transport remains normal[18,19,23-25]. Recent studies of Dukelow *et al.*[26] have shown that an IUCD has no effect on sperm capacitation in rabbits.

Tubal Events

Acceleration of ova passage — It has been shown that in rhesus monkeys superovulated with exogenous gonadotrophin and fitted with IUCD the tubal transport of ova is markedly speeded up, so much so that ova could no longer be found in such animals in the tubes 5 hr after the expected time of ovulation, compared to approximately 3 days in similarly superovulated controls not fitted with the IUCD[23]. Ova could, however, be recovered following unilateral tubal ligation and even from the uterus of non-ligated females provided they were examined early enough. Fertilized ova could not be recovered from the tubal and uterine washings of these animals, but were found in controls.

The validity of these findings was examined recently in unstimulated normally cyclic and spontaneously ovulating rhesus monkeys[27,28]. It was observed that there was no marked difference in the rate of recovery of ova from tubes of normal and

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IUCD-fitted animals. It was concluded that if there was any speeding up in the tubal passage of ova due to he presence of an IUCD in spontaneously ovulating monkeys, it was far less pronounced than that reported by Mastroianni and Hongsonand[23]. Eckstein[29], commenting on the studies of Mastroianni and Hongsonand, pointed out that the gonadotrophin stimulated ovaries of these monkeys produce excessive amounts of estrogen and progesterone. It was, therefore, not surprising that such superovulated ova should pass rapidly through the tubes and the uterus; the possibility also remained that due to such excessive production of sex hormones the endometrial sensitivity was disturbed.

One of the earliest of modern theories advanced to explain the mode of action of IUCDs in human is that the device stimulates tubal motility as a result of which the ovum is rushed through the tubes and arrives prematurely in the uterus in a condition unfit for implantation[30,31]. The endometrium, in its turn, does not have sufficient time to undergo full progestational transformation necessary for reception of the blastocyst. The evidence frequently offered in favour of this theory is the small number of tubal pregnancies that have been encountered in women fitted with IUCDs, the incidence being about one-twelfth of the rate recorded in normal populations[32]. In this connection, the following reports merit critical consideration:

(i) No evidence of increased tubal peristalsis or mechanical obstruction of the tubes could be found in women fitted with IUCDs[33].

(ii) A low rate of tubal pregnancy in women may validate the rapid ova passage theory but does not actually confirm it. Most of the women using IUCD are highly fertile and have had many consecutive uterine pregnancies; thus a low incidence of tubal pregnancy can be expected. Whether the reported rate of tubal pregnancy is unusual in such women can be determined only by comparing their incidence with that for women of similar age and parity who are not using IUCD, rather than with the rate for total population[32]. Chen and Ta-Ko[34] reported six cases of tubal pregnancy in women fitted with IUCD during a 7-month period. Willson *et al.*[35] described 3 ectopic pregnancies out of 623 women fitted with IUCD. Denny[36] also recorded a case of tubal pregnancy. Tietze[37] provided statistical evidence in support of the rapid ova transport theory. He estimated that in 22,400 women wearing IUCD with an aggregate of more than 300,000 women months of use, 588 pregnancies occurred with the device *in situ*. Of these, 26, or 1 in 23, pregnancies were ectopics. In normal population, a conservative estimate of tubal pregnancy would be between 0·8 and 1·2 pregnancies per 100 women per year. With approximately 25,000 women using the IUCD, between 200 and 300 ectopic pregnancies would be expected, but only 26 did in fact occur. While the incidence of ectopic pregnancies is very high in relation to the total number of pregnancies, it is very low in relation to the number expected on the assumption that the mode of action of IUCD is at the uterine level. Thus these statistical findings indicate that the IUCD acts by speeding up the transport of ova through the fallopian tubes.

(iii) Bonney *et al.*[18] found no evidence of rapid transport of ova through the tubes in women wearing IUCD. On the contrary, the recovery rate of ova from the tubes in IUCD-fitted women was somewhat higher than in control women.

(iv) An IUCD does not cause any noteworthy biochemical changes in the tubal tissue of rhesus monkeys except for some increase (28 per cent) in oxygen consumption rate during the proliferative phase 90 days post-insertion[38]. However, this does not involve any alterations in normal metabolism of the tubes, and probably is a biochemical expression of transitory mild trauma to the genital tract caused by a foreign body. This is indicated by a normal oxygen consumption rate of the tubes 545 days post-insertion[17]. Similarly, the biochemical composition of the tubal fluid of rabbits does not show any noteworthy alterations due to the presence of an IUCD[39].

(v) The insertion of a surgical silk suture directly into one tube of rabbits (the suture was inserted through the isthmic end of the ampullary-isthmic junction, passed along the lumen and then brought out through the same wall at the ampulla end about 2 cm. above the point of entry and the two ends of the suture were tied into a knot. The animals were mated 45 days post-insertion) stopped pregnancy in 45 per cent of the animals[40]. The number of foetuses was significantly low in the treated tube side, although the number of corpora was virtually the same in the two ovaries as revealed by laparotomy on fifteenth day of pregnancy. This showed that about 67 per cent of ova somehow failed to implant or there was a foetal loss of this magnitude.

In rabbits fitted with IUCD, a high foetal loss has been recorded between the 10th and 27th day of pregnancy in addition to a failure in ova implantation[41-43]; the latter is due to a local effect of the device, but the foetal loss during the second half of pregnancy is observed in both control and treated horns[26]. Post-coital ligation of the tubes has been reported to impede development of the blastocysts[44]. Whether the absence of pregnancy in the treated side horn observed in this study was due to a foetal loss occurring between 10th and 15th day *post-coitum*, or inhibition of blastocyst development due to the presence of an intratubal device could not be determined. The same comment would hold good for a possible effect of the device on tubal transport of ova. However, Corfman and Segal[45] have recently shown that an intratubal suture does indeed speed up ova passage in this species.

It thus appears that there is as yet no firm experimental or clinical basis for the view that the tubal passage of ova is considerably accelerated in the presence of an IUCD. Even if this is the case, little is known as to how such speedy transport is achieved. It has been suggested that an IUCD provokes a state of hyperestrogenism, or an increased sensitivity of the genital tract to estrogen[46-48]. There is also some indirect evidence (like a high urinary FSH excretion rate) of such hyperestrogenism in women wearing IUCD[20]. Accordingly, it has been opined that increased secretion of estrogen by the ovary in the presence of an IUCD may be responsible for such rapid transport of ova; this property of

estrogens is now well authenticated although precisely how the effect is exerted is not known[47].

Recently, Kar *et al.*[49] investigated the tubal sensitivity of IUCD-fitted ovariectomized rhesus monkeys to exogenous estrogen, but could not find any ponderal or histologic evidence of an increased responsiveness. Biochemically, estrogen did not cause any increase in the concentration of DNA, acid-soluble phosphates and total lipids in the tubes which it did significantly in animals not wearing the IUCD. However, the implication of these biochemical changes in relation to a rapid transport of tubal ova is difficult to assess. Moreover, the actual tubal transit time of human ova has not been determined with certainty[50].

In the same study[49], the uterus did not show any increased or decreased sensitivity to estrogen. Tamada and Sturgis[51] also reported no effect of IUCD on uterine responsiveness of ovariectomized rhesus monkeys to estrogen and progesterone. However, at the points of contact of the device the endometrium showed squamous metaplasia of the epithelium. Similar changes have been recorded in women fitted with IUCD for 1-2 years[51].

Retardation of ova passage — Doyle and Margolis[52] observed that in mice IUCD retards the tubal passage of ova on the treated side and inhibits implantation in the control uterine horn. This shows that an IUCD may act through two different points in the reproductive mechanisms in the same species.

Fertilization — Interference with fertilization has been demonstrated clearly only in sheep fitted with IUCD and this is evidently achieved by a retardation of sperm transport[21]. A similar disturbance in fertilization probably occurs in artificially inseminated cows but not in normally mated ones[6,53]. However, in sheep, ova recovered from IUCD-fitted females can be transferred into the uteri of normal host ewes and following mating of the host, they will be fertilized and implanted[21]. This shows that in this species IUCD does not affect fertilizability of the ovum.

It is not known whether the fertilization process or fertilizability of ova are disturbed in women wearing IUCD even though a pronuclear ovum has been recovered from tubal washings of such individuals[50,54].

Implantation

The most widely held view about the mode of action of IUCDs is that they somehow prevent implantation of the blastocyst. In this connection, an interference with the blastocyst or the uterine components of the implantation process including the luminal fluid milieu, provocation of unphysiologic motility of the uterus, neurogenic disturbances, inflammation, physical coverage of the endometrial surface and the role of the cervix have been considered. However, a species difference in the extent of influence of IUCD on the implantation process should be kept in view. In guinea-pigs, for instance, a silk suture device does not interfere consistently with implantation[55].

Blastocyst component and the uterine fluid milieu — There is little published information on the effect of IUCDs on biochemistry, metabolism, morphology and ultrastructure of the blastocyst. Several authors recovered degenerated blastocysts from the uterine horn of rats fitted with a silk suture device[56]. Recently, Dukelow *et al.*[26] reported that fluid aspirated from the blastocyst of rabbits recovered from the IUCD-fitted uterine horn contains 38 per cent less carbohydrates than that collected from the blastocyst from the control horn. It is interesting that the uterine fluid from the IUCD-fitted horn also contains 38 per cent less carbohydrates than that from the control horn[26]. On the other hand, some knowledge is available regarding the uterine fluid milieu. Kar *et al.*[46], in their detailed biochemical studies on the uterine luminal fluid of rats in the presence of a silk suture device, could not find any change in *p*H of the fluid (also Marcus *et al.*[57]), but the volume was reduced by about 50 per cent with a marked change in consistency. This was apparently a dehydration effect since the concentration of nitrogen, lactic acid, total lipids, phospholipids and bases, and free and ester sterols increased almost twofold. There were also some interesting changes in electrolytes. Paper electrophoretic studies revealed the passage of a protein into the fluid having the same electrophoretic mobility as albumin. The latter was consistently absent in the control horn fluid as revealed by this technique. This protein comprised about 50 per cent of the total protein of the fluid as measured by planimetry. This was probably due to foreign body reaction and apparently contributed to the viscosity of the fluid which was normally thin and opalescent in consistency. A notable effect of such a high concentration of an albumin-like protein would be a rise in overall osmotic tension of the fluid. If it is assumed that this protein is albumin, with molecular weight 68000, a representative sample of the fluid containing 3 g./100 g. of this protein would exert an oncotic pressure alone of about 8 mm. Hg. This, together with the increased osmotic pressure due to elevated non-protein constituents, may expose the blastocyst to an uterine luminal milieu with considerable dehydrating influence; obviously, such a milieu is not expected to be conducive to blastocyst implantation.

According to Corfman and Segal[45], leucocytic infiltration of the endometrium and the lumen may play an important role in such biochemical changes in the luminal fluid and degeneration of the blastocyst prior to nidation. Depending upon the species, the leucocytic invasion occurs in the presence or absence of bacterial infection[58]. As judged by estimation of lysozyme in the uterine lumen of rats and rabbits, the leucocytes release their contents into the uterine fluid. It is believed that some substance derived from leucocytes may exert toxic effects on the blastocysts or on spermatozoa[58].

Dukelow *et al.*[26,59] studied the biochemical changes in the uterine and tubal fluid of rabbits at the time of IUCD-induced embryonic mortality[41]. They observed that per cent dry weight, protein and amylase content, and lysozome activity of the fluids were reduced in the presence of IUCD. The volume and *p*H of the tubal fluid were virtually unchanged. However, the sialic acid and carbohydrate contents of the tubal fluid were increased, while in the uterine fluid the last constituents were decreased. The IUCD had no effect on free amino acid pattern (aspartic acid, glycine, serine, valine and leucine)

of the tubal fluid. In the uterine fluid of the IUCD-fitted horn, serine and glutamic acid were identified as free amino acids but aspartic acid was absent. In the control horn, apart from the first two amino acids, aspartic acid was also present. It was suggested that in this species there was increased proteolytic activity and alteration in levels of carbohydrate-sialic acid moieties of the uterine and tubal fluids at the time of IUCD-induced embryonic mortality. It was apparently contradictory that the IUCD had no effect on total proteolytic enzyme activity of the fluids[59].

In the human female, there is evidence of some changes in the uterine secretions in the presence of an IUCD. Americh[60] noted that IUCD causes profuse secretion of the endometrial glands which fill the lumen. He believed that this was an impediment to implantation of the blastocyst. Vorys *et al.*[20] observed that women wearing the Margulies spiral who had no pain, discharge or bleeding often had scanty endometrial secretions. Hall *et al.*[61] reported no change in total protein concentration of the secretion in women fitted with IUCD, but the total carbohydrate concentration recorded an appreciable rise. However, Kar (Kar, A. B., unpublished observations) recently found about 200 per cent increase in total protein concentration of the uterine fluid of women fitted with the loop for 1-2 years. Stone[62] noted the presence of neutrophils in the fibrin of the endometrial glandular lumen in women fitted with IUCD which indicated some changes in endometrial secretion. Bonney *et al.*[18] found that the endometrial secretions became thick and mucoid around the Margulies coil during the proliferative phase.

Endometrial component—Inhibition of decidualization: An evidence frequently cited to explain the mechanism of the anti-implantation effect of IUCD, particularly in rats, is that it inhibits the process of decidualization[43,56,63], although Segal[64] holds a contrary opinion. However, divergent views have been expressed as to how the anti-decidualization effect is achieved. Psychoyos[65] showed that trauma caused an increase in uptake of progesterone-^{14}C by the rat uterus. He suggested that the presence of IUCD has the same effect as trauma *vis-à-vis* progesterone uptake by this organ. In other words, the uterus becomes more sensitive to progesterone. If this period of progesterone uptake precedes estrus, estrogen liberated on this day will complete the progesterone-estrogen sequence, so critical for decidualization, rather prematurely; so much so, that the period of uterine receptivity will ensue at a time when the ova are still in the Fallopian tubes. When they reach the uterus it has already passed into the non-receptive stage and thus implantation will not occur. If both uterine horns of the rat are traumatized during the sensitive period, the control horn will respond normally, whereas the IUCD-fitted one will show a decreased vascular response. Psychoyos considers this to be due to the non-receptive stage of horn provoked by an increased sensitivity to progesterone circulating before estrus. For this reason the uterus has to be fitted with the device before estrus to achieve the inhibitory effect. One day may make all the difference; if the device is inserted during estrus no anti-implantation effect is seen. However, according to Joshi[66], IUCD inhibits decidualization in rats by reducing uterine sensitivity to progesterone.

Potts[67] reported two cases of pregnancy in women during the particular cycle in which the IUCD was inserted. He believed that this was an evidence in support of Psychoyos' view since the device was not there early enough to upset the timing of the cycle. According to Psychoyos[65], the presence of IUCD in women is necessary for a short period before ovulation to bring about precocious endometrial sensitization to progesterone (as in rats) leading to an ova-endometrial 'asynchrony'. Even low-grade injuries make the endometrium (rat) hypersensitive to progesterone[68].

Laumus and Farooq[69] did not observe any effect of IUCD on uterine uptake and retention of 1,2-H^3-progesterone in rats (cf. Joshi[70]). Kar *et al.*[46] observed increased sensitivity of the uterus to estrogen in this species in the presence of IUCD. This may contribute to an imbalance in the optimal responsiveness of the uterus to the two critical hormones involved in the decidualization process. Psychoyos[65] considers changes in uterine fluid also to be concerned in the inhibition of decidualization. According to Craig[71] an increase in mass of the uterus and maturation of the cellular elements of the submucosa with dispersion of collagen are responsible for the inhibition of decidualization in rats.

Shelesnyak[72] believes that IUCD causes premature depletion of the uterine histamine store so that very little or none is available at the proper time to induce decidualization. Actual estimations have shown an initial low histamine content of the IUCD-fitted horn followed by a rise, as compared to the control horn[45,68]. Roy Chowdhury's[73] findings on the increase in the number of uterine mast cells in animals fitted with a silk suture tend to support this concept. However, in cows, an IUCD has no effect on the total number of mast cells in the adjacent endometrium[74]. An increase in the total endometrial mucopolysaccharides probably secondary to focal inflammation, has also been recorded in cows in the presence of IUCD[53]. High doses of estrogen are known to evoke similar changes in the mast cells of the guinea-pig endometrium[75]. Thus, it is not unlikely that in rats an IUCD prevents implantation both by provoking adverse physico-chemical changes in the uterine luminal fluid milieu and by inhibiting the process of decidualization. However, IUCDs have no effect on the decidual response in ovariectomized and hormonally treated rhesus monkeys[45].

Potts[67] made the interesting suggestions that (i) a device might merely hold the epithelium apart mechanically so that in species with small blastocysts such as in human, the blastocysts simply fall out and do not come in contact with the endometrium to implant, and (ii) the trophoblast preferentially implants on the plastic IUCD rather than on the endometrium. Mouse blastocysts cultured *in vitro* stick remarkably well on plastic dishes; the trophoblast comes into intimate contact with the plastic material and spreads out very rapidly in all directions. Dukelow *et al.*[26] recently reported implantation of the blastocysts directly on the plastic device in two rabbits which developed apparently normally

till the fourteenth day and then (by the twenty-third day) resorbed. However, Meyer[76] was unable to find any such implantation on the devices themselves. This possibility is not valid for silver or stainless steel rings[68,76].

Provocation of decidualization: Since decidua formation is known to prevent implantation in rats, this mechanism has been invoked to explain the anti-implantation effect of IUCD in this species[77,78]. However, Doyle and Margolis[56] and Kar *et al.*[79] did not find any evidence of deciduoma formation in this species in the presence of a silk thread.

Bonney *et al.*[18] recorded a rather premature predecidual type of reaction of an abnormally fibrous nature in the endometrium of women fitted with IUCD. They considered this as a manifestation of the failure of the endometrium to undergo biochemical maturation which provides the most optimal uterine environment for implantation. They further added that such biochemical maturation was synchronous with that taking place in the ovum and in other sites of the neuro-endocrine system concerned with the implantation process. As an evidence of such disturbance in biochemical maturation it was observed that IUCD retards the increase in non-phospholipid to phospholipid ratio of the endometrium found to occur coincidentally with ovulation[80]. Conceivably, adverse physico-chemical changes in the uterine fluid milieu may also retard such biochemical maturation of the preimplantation blastocyst and make it unfit for implantation.

According to Grafenburg[2] a ' hyperdecidual ' condition of the endometrium provoked by the device is responsible for implantation failure. Jessen *et al.*[81] and Rozin *et al.*[82] recorded the occurrence of decidual tissue in women fitted with IUCD. Several investigators reported asynchrony in histologic dating of the endometrium and the stage of the cycle in women fitted with IUCD; the endometrium lagged behind the normal cycle[19,83,84]. A recent electron microscopic study provided interesting evidence of such delay in endometrial maturation in the presence of IUCD[85]. Such asynchronous endometria may also be unfit for implantation.

Stimulation of uterine motility — In rats IUCD does not provoke excessive electrical activity of the myometrium nor alters its sensitivity to oxytocin[86,87]. Oxytocin release is not disturbed either[87]. However, Marcus *et al.*[57] reported an increase in uterine motility in this species in the presence of a silk suture. In rabbits, no consistent suppressive or stimulatory effect of IUCD on uterine motility could be recorded in *in vivo* studies[88]. In rhesus monkeys, there is a possibility that the immediate effect of a device is to convert a given motility pattern into one characteristic of menstruation and labour[25]. This effect is, however, transitory and eventually results in slight accentuation of the normal motility pattern of the uterus. On the other hand, Martin and Eckstein[89] recorded a depressive effect of IUCD on the frequency and amplitude of the uterine contractions in this species.

Bengtsson and Moawad[90] investigated the motility of the human uterus *in vivo*, twice weekly, by means of an intrauterine catheter connected with a pressure recorder. They observed that prelabour type of contractions normally appeared about the twenty-fifth day of the cycle, but these developed about the nineteenth day of the cycle after the insertion of an IUCD. They suggested that the occurrence of such contractions at about the time of implantation explains the contraceptive action of the IUCD. Marcus *et al.*[57] also noted a stimulation of uterine motility in women fitted with IUCD. However, Johnson *et al.*[91] did not find any effect of the device on the frequency and amplitude of uterine contractions in women. Whether such acute stimulatory effect of IUCD on uterine motility persists throughout its period of residence remains to be determined. In this connection, any hemodynamic changes in the uterus also merit consideration. According to a recent report an acute increase in myometrial activity in women after IUCD insertion diminishes with time[92].

Neurogenic factors — The possibility of involvement of neurogenic factors in the mode of action of IUCD has been considered in rats and sheep. Segal[64] achieved normal implantation in the IUCD-fitted horn of rats by severing its sympathetic nervous connections. Wishik[93], citing studies on sheep, reported that when an inflated balloon-like object of the size of an embryo was fitted into one uterine horn, the contralateral horn did not become pregnant. When the balloon-fitted horn was resected by cutting at both ends and removing all nerve connections, and then re-sutured back without apparently restoring the nerve supply the contralateral horn did accept a pregnancy. These studies suggest a possible neurogenic involvement in the mode of action of IUCD in this species.

Toth *et al.*[94] observed that pelvic parasympathectomy caused vaso-constriction and an imbalance of the homeostatic vascular mechanisms in dogs through the resultant sympathetic dominance. The vicious circle thus created led to a diminished blood flow to the uterus, hypoxia and impeded nutrient supply. The net effect on early implantation stages and the foetus was disastrous. It may be suggested that IUCD somehow causes similar sympathetic dominance and thereby disturbs the optimal hemodynamics of the endometrium, which is so critical for the implantation process. There is some evidence of a reduced capillary permeability of the rat uterus in the presence of an IUCD[25]. Segal's[64] findings in rats are also suggestive. Bland and Donovan[95] are, however, critical of the neurogenic theory since, according to them, the " denervation of a segment of the uterus as done in sheep must inevitably interfere with the normal activities of the endometrium by disrupting its blood supply ". Apparently, any neurogenic involvement in the mode of action of IUCD may be only one facet of a more complicated mechanism.

Inflammation — According to Greenwald[96], the endometrial inflammation caused by IUCDs in rats is primarily responsible for the anti-implantation effect and this condition increases the uterine motility causing expulsion of the pre-implantation blastocyst *per vaginum*. However, Parr and Segal[97] and Sudha *et al.*[98] consider endometrial inflammation as an unlikely cause for implantation failure in this species.

A mild inflammatory condition of the endometrium is often encountered in women wearing IUCD[32,81,99,100]. Jessen *et al.*[81] opined that this condition may have some bearing on the mode of action of the devices. However, the current consensus is that such inflammatory changes represent a 'sterile irritation' of the endometrium due to the presence of a foreign body and have little to do with its mode of action[25,32,99,100]. However, Corfman and Segal[45] considered such changes in the endometrium (including transitory bacterial contamination which occurs almost universally immediately after insertion[100]) as being sufficient to explain the prevention of uterine pregnancies.

Coverage of endometrial surface — The view that physical coverage of endometrial surface by IUCD is responsible for preventing implantation in rabbits[3] has subsequently proved untenable[41,101]. This is also probably true of other species including human[25]. In the latter there is enough exposed endometrium in spite of the presence of an IUCD (such as the Lippes loop, Hall-Stone stainless steel ring and Zipper nylon ring), but even then pregnancy does not usually occur.

Nevertheless, this view has found support from time to time. Meyer[76] observed that when a silk suture was placed either in the upper middle or lower one-third of the rat uterine horn, implantation did occur in 25-40 per cent cases. If the suture is inserted from the mesometrial to the anti-mesometrial surface at one point only, implantation was not prevented. This suggests that maximum contact of the foreign body with the endometrium is necessary to prevent implantation. Similarly, in rabbits Ledger *et al.*[14] noted that complete prevention of implantation is achieved in the area of the endometrium with which a device is in intimate contact.

Role of cervix — Speilburger and Olewine[102] reported that a silk suture inserted in the cervical region of rats reduced the number of implantations and caused foetal degeneration. However, in women, IUCD has no effect on the cervical mucus[20,103], or histology of the cervix[99].

Mode of Action of IUCD and Post-Insertion Bleeding

Early studies by Meyer[104] and recent studies by Willson *et al.*[84] and Israel and Davis[99] in women, and Kar and Chandra[105,106] in rhesus monkeys, revealed certain vascular and other changes in the endometrium during the IUCD post-insertion bleeding episodes. These changes are virtually alike in both species and consist of edema and congestion of the superficial layers of the endometrium; patchy to marked denudation of the surface epithelium; development of large thin-walled vascular channels in the superficial layers which do not bulge over the surface nor show signs of rupture; passage of blood (and probably also lymph) from these channels into lumen, particularly noticeable at places where the surface epithelium has denuded; passage of blood from capillaries and probably also lymph focally in the stroma; compression of the endometrium at places without necrosis, and with or without ulcerogenicity; and occasional presence of a debris of denuded epithelial cells, blood and lymph in the lumen. Similar changes have been observed in the endometria of sexually immature rhesus monkeys which also show such uterine bleeding after insertion of IUCD[106]. This suggests that the stimulus provoking bleeding acts directly (from the IUCD) on the endometrial vasculature and not via any hormonal mechanisms. On biochemical grounds[16,17,107,108] it appears that this stimulus is temporary, mild trauma to the endometrium. This is suggested particularly by a transitory rise in the oxygen consumption of the endometrium without any disturbance in its basic metabolic pattern. The nature of such vascular changes appears to be similar to those occurring in the blood vessels of a tissue under trauma. The post-insertion bleeding in women and in rhesus monkeys may indeed be traumatic. If this is so, it is conceivable that in the provocation of such vascular changes by the IUCD leading to bleeding, a transitory histamine surge may be involved at some stages[109]. It is also possible that the significance of an increased oxygen level is to dispose off such traumatically liberated histamine by oxidation. As pointed out before, histamine has been implicated in the mode of action of the IUCD[72].

Conclusion

From a critical consideration of the currently available knowledge, it appears that IUCD prevents pregnancy by acting simultaneously and synchronously on several vulnerable points in the reproductive mechanisms. A similar mode of action has been envisaged for the steroidal contraceptives[47]. It has been possible to achieve effective contraception with some of the progestational steroids through a dissociable action on a particular point of impact; this is done by simple dosage manipulation[110]. By such wilful dissociation, the 'load' on different points of impact may be evenly disturbed during the prolonged periods of the use of a contraceptive with minimization of chances of disruption of the homeostatic reproductive mechanisms. It may be possible to develop IUCDs of suitable design and material which would act in such dissociable manner with better efficacy and minimum of side effects. Further knowledge about their mode of action may help to realize such possibility.

Summary

In different species, the intrauterine contraceptive devices (IUCD) influence different points in the reproductive mechanisms like ovulation, corpus luteum function, sperm transport, tubal passage of ova, fertilization and implantation. Even a particular process like implantation may be affected through multiple pathways like ovo-endometrial maturation, uterine luminal fluid milieu, decidualization, myometrial contractility, neurogenic factors, inflammatory changes in the endometrium, coverage of endometrial surface, and cervical alterations. No common primary point of impact has been identified in the reproductive mechanisms to explain the mode of action of IUCDs in different species. Accordingly, it is not unlikely that the devices prevent pregnancy by acting simultaneously and

synchronously on several vulnerable loci in the reproductive mechanisms.

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References

1. HAIRE, N., *Br. med. J.*, **11** (1929), 1133.
2. GRAFENBURG, E. VON, *Rep. int. med. group for investigation of contracept., London*, 1930, 12.
3. CARLETON, H. M. & PHELPS, H. J., *J. Obstet. Gynaec. Br. E.*, **40** (1933), 81.
4. HAVRANEK, F., DYKARA, H. & TICHY, M., *J. Reprod. Fert.*, **14** (1967), 15.
5. BUCH, N. C., SHUKLA, K. P. & HAWK, H. H., *Proc. 5th int. congr. anim. reprod. (Toronto)*, 1965.
6. HAWK, H. W., CONLEY, H. H., BRINSFIELD, T. H. & RIGHTER, H. F., *Proc. 2nd int. conf. intraut.c ontracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
7. GINTHER, O. J., WOODY, C. O., JANAKIRAMAN, K. & CASIDA, L. E., *J. Reprod. Fert.*, **12** (1966), 193.
8. GINTHER, O. J., POPE, A. L. & CASIDA, L. E., *J. Anim. Sci.*, **25** (1966), 472.
9. GINTHER, O. J., MAHAJAN, S. & CASIDA, L. E., *Proc. Soc. exp. Biol. Med.*, **123** (1966), 775.
10. CERRITIS, R. C. & HAWK, H. W., *J. Anim. Sci.*, **25** (1966), 1266.
11. RATHMACHER, R. P., ANDERSON, L. L., KAWATA, K. & MELAMPY, R. M., *J. Reprod. Fert.*, **13** (1967), 559.
12. JANAKIRAMAN, K. & CASIDA, L. E., *J. Reprod. Fert.*, (in press).
13. GINTHER, O. J., HAWK, H. W. & CASIDA, L. E., *J. Anim. Sci.*, **25** (1966), 1262.
14. LEDGER, W. J., VIRKAR, K. D. & IRVIN, L. A., *Obstet. Gynec., N.Y.*, **28** (1966), 321.
15. LEDGER, W. J. & BICKLEY, J. E., *Obstet. Gynec., N.Y.*, **27** (1966), 558.
16. KAR, A. B., CHOWDHURY, S. R., KAMBOJ, V. P., CHANDRA, H. & CHOWDHURY, A. R., *Int. J. Fert.*, **10** (1965), 321.
17. KAR, A. B., KAMBOJ, V. P., CHOWDHURY, S. R., CHANDRA, H. & CHOWDHURY, A. R., *Am. J. Obstet. Gynec.*, **98** (1967), 194.
18. BONNEY (Jr), W. A., GLASSER, S. R., CLEWE, T. R., NOYES, R. W. & COPPER, C., *Am. J. Obstet. Gynec.*, **96** (1966), 101.
19. SUJAN-TEJUJA, S., VIRICK, R. K. & MALKANI, P. K., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
20. VORYS, N., DENEEF, J., BOUTSELIS, J. G., DETTMAN, F. G., SCOTT, W. P., STEVENS, M. C. & BESCH, P. K., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
21. HAWK, H. W., *J. Reprod. Fert.*, **10** (1965), 267.
22. LAKE, P. E. & GILBERT, A. B., *J. Reprod. Fert.*, **8** (1964), 272.
23. MASTROIANNI (Jr), L. & HONGSONAND, C., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
24. MORGENSTERN, L. L., ORGBEIN-CREIST, M. C., CLEWE, T. H., BONNEY, W. A. & NOYES, R. W., *Am. J. Obstet. Gynec.*, **96** (1966), 44.
25. *Basic and clinical aspects of intrauterine contraceptive devices*, Technical Report Series No. 332 (World Health Organization, Geneva), 1966.
26. DUKELOW, W. R., PERRY, H. A. & WILLIAMS, W. L., *Fert. Steril.*, **18** (1967), 557.
27. ECKSTEIN, P., *Abstracts of papers presented at the 8th int. conf. plann. parent., Santiago* (The International Planned Parenthood Federation, London), 1967.
28. KELLY, W. A. & MARSTON, J. H., *Nature, Lond.*, **214** (1967), 735.
29. ECKSTEIN, P., *Recent researches in egg implantation*, Ciba Foundation Study Group No. 23 (J. & A. Churchill Ltd, London), 1966.
30. ALLEN, E. S. & BROWN, W. E., *Proc. Ark. Med. Soc.*, **61** (1964), 141.
31. MARGULIES, L. C., *Obstet. Gynec., N.Y.*, **24** (1964), 515.
32. WILLSON, J. R., *Pacific Med. Surg.*, **73** (1965), 44.
33. SIEGLER, A. M. & HELLMAN, L. M., *Obstet. Gynec., N.Y.*, **23** (1964), 173.
34. CHEN, R. R. & TA-KO, K., *Br. med. J.*, **1** (1966), 1297.
35. WILLSON, J. R., BOLLINGER, C. C. & LEDGER, W. J., *Am. J. Obstet. Gynec.*, **70** (1964), 726.
36. DENNY, F., *Br. med. J.*, **1** (1966), 1418.
37. TIETZE, C., *Br. med. J.*, **2** (1966), 302.
38. KAR, A. B., CHOWDHURY, S. R., KAMBOJ, V. P., CHANDRA, H. & CHOWDHURY, A. R., *Endokrinol.*, **49** (1965), 137.
39. KAR, A. B., KAMBOJ, V. P., CHOWDHURY, S. R. & CHOWDHURY, A. R., *Indian J. exp. Biol.*, **3** (1965), 268.
40. KAR, A. B. & KAMBOJ, V. P., *Ind. J. exp. Biol.*, **4** (1966), 119.
41. ADAMS, C. E. & ECKSTEIN, P., *Fert. Steril.*, **16** (1965), 508.
42. BROWN, E. & FOOTE, R. H., *J. Reprod. Fert.*, **12** (1966), 373.
43. MARSTON, J. H. & CHANG, M. C., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
44. ADAMS, C. E., *J. Endocrinol.*, **16** (1958), 283.
45. CORFMAN, P. A. & SEGAL, S. J., *Am. J. Obstet. Gynec.*, (in press).
46. KAR, A. B., GOSWAMI, A., KAMBOJ, V. P. & CHOWDHURY, S. R., *Steroids*, **4** (1964), 159.
47. PINCUS, G., *The control of fertility* (Academic Press Inc., New York), 1965.
48. JANAKIRAMAN, K., SHUKLA, K. P., GADGIL, B. A. & BUCH, N. C., *J. Reprod. Fert.*, **11** (1966), 148.
49. KAR, A. B., KAMBOJ, V. P., CHANDRA, H. & KARKUN, J. N., *Indian J. exp. Biol.*, **4** (1966), 171.
50. NOYES, R. W., CLEWE, T. H., BONNEY, W. A., BURRUS, S. B., DEFEO, V. J. & MORGENSTERN, L. L., *Am. J. Obstet. Gynec.*, **96** (1966), 157.
51. TAMADA, T. & STURGIS, S. H., *Obstet. Gynec., N.Y.*, **28** (1966), 793.
52. DOYLE, L. & MARGOLIS, A. J., *J. Reprod. Fert.*, **11** (1966), 27.
53. HAWK, H. W. & COOPER, B. S., *J. Anim. Sci.*, **25** (1966), 1267.
54. NOYES, R. W., DICKMANN, Z., CLEWE, T. H. & BONNEY, W. A., *Science, N.Y.*, **147** (1965), 744.
55. DEANESLY, R., *Recent researches in egg implantation*, Ciba Foundation Study Group No. 23 (J. & A. Churchill Ltd, London), 1966.
56. DOYLE, L. & MARGOLIS, A. J., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
57. MARCUS, L. S., MARCUS, C. C. & WILSON, H. K., *Obstet. Gynec., N.Y.*, **27** (1966), 238.
58. PARR, E., SCHAEDLER, R. W. & HIRSCH, J. G., *J. exp. Med.*, **126** (1967), 523.
59. DUKELOW, W. R., PERRY, H. A., CHERWOFF, H. N. & WILLIAMS, W. L., *J. Dairy Sci.*, **49** (1966), 731.
60. AMERICH, I., *Ciba Symp.*, **11** (1963), 13.
61. HALL, H. H., SEDLIS, A., CHABON, I. & STONE, M. L., *Am. J. Obstet. Gynec.*, **93** (1965), 1031.
62. STONE, H. L., *Am. J. Obstet. Gynec.*, **93** (1965), 8021.
63. FAROOQ, A., *Proc. workshop conf. on endocrinol., New Delhi*, 1965, 69.
64. SEGAL, S. J., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
65. PSYCHOYOS, A., *Recent researches on egg implantation*, Ciba Foundation Study Group No. 23 (J. & A. Churchill Ltd, London), 1966.
66. JOSHI, S., *Indian J. exp. Biol.*, **5** (1967), 168.
67. POTTS, M., *Recent researches on egg implantation*, Ciba Foundation Study Group No. 23 (J. & A. Churchill Ltd, London), 1966.
68. SHELESNYAK, M. C., *Recent researches on egg implantation*, Ciba Foundation Study Group No. 23 (J. & A. Churchill Ltd, London), 1966.
69. LAUMUS, K. R. & FAROOQ, A., *Indian J. exp. Biol.*, **5** (1967), 12.

70. JOSHI, S., *Indian J. exp. Biol.*, **5** (1967), 68.
71. CRAIG, J. M., *Fert. Steril.*, **18** (1967), 466.
72. SHELESNYAK, M. C., *Agents affecting fertility* (Little Brown & Co., London), 1966.
73. ROY CHOWDHURY, R., *Proc. conf. reprod. biol.* (The Central Family Planning Institute, New Delhi), 1966.
74. HAWK, H. W., CONLEY, H. H. & BRINSFIELD, T. H., *Fert. Steril.*, (in press).
75. IVERSEN, O. H., *Acta Path. Microbiol. Scand.*, **56** (1962), 245.
76. MEYER, R. K., *Recent researches on egg implantation*, Ciba Foundation Study Group No. 23 (J. & A. Churchill Ltd, London), 1966.
77. EICHNER, E., *Science, N.Y.*, **140** (1963), 1136.
78. NICHMAN, M. Z., *Am. J. Physiol.*, **186** (1956), 6.
79. KAR, A. B., KAMBOJ, V. P. & DATTA, J. K., *J. Reprod. Fert.*, **8** (1964), 139.
80. GLASSER, S., *Fed. Proc.*, **56** (1967), 536.
81. JESSEN, D. A., LANE, R. E. & GREENE, R. R., *Am. J. Obstet. Gynec.*, **85** (1963), 1023.
82. ROZIN, S., SACKS, M. I. & SHENKER, J. G., *Am. J. Obstet. Gynec.*, **97** (1967), 197.
83. AQUILERA, E. & VALENZUELA, E., *Abstracts of papers presented at the 8th int. conf. planned parenthood, Santiago* (The International Planned Parenthood Federation, London), 1967.
84. WILLSON, J. R., LEDGER, W. J. & ANDROS, G. J., *Am. J. Obstet. Gynec.*, **93** (1965), 802.
85. WYNN, R., *Science, N.Y.*, **156** (1967), 508.
86. PARR, E., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
87. ROY CHOWDHURY, R. & TARAH, T. K., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
88. KAR, A. B., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
89. MARTIN, C. B. & ECKSTEIN, P., *Am. J. Obstet. Gynec.*, **94** (1966), 415.
90. BENGTSSON, L. P. & MOAWAD, A. H., *Lancet*, **6** (1966), 146.
91. JOHNSON, W. L., BREWER, W. E. & BREWER, L., *Obstet. Gynec., N.Y.*, **28** (1966), 326.
92. BEHRMAN, S. J., *Am. J. Obstet. Gynec.*, (in press).
93. WISHIK, S., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
94. TOTH, A., MCEWEN, R. & SHABANAH, E. H., *Fert. Steril.*, **15** (1964), 263.
95. BLAND, K. P. & DONOVAN, B. T., *Recent advances in reproductive physiology* (Academic Press Inc., New York), 1966.
96. GREENWALD, G. S., *J. Reprod. Fert.*, **9** (1965), 9.
97. PARR, E. & SEGAL, S. J., *Fert. Steril.*, **17** (1966), 648.
98. SUDHA, S., CHAKRAVARTY, R. N. & CHOWDHURY, R. R., *Indian J. med. Res.*, **57** (1967), 1015.
99. ISRAEL, R. & DAVIS, H. J., *J. Am. Med. Assoc.*, **195** (1966), 764.
100. MOYER, D. & MISHELL (Jr), D. R., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
101. ZIPPER, J., GARCIA, M. L. & PASTENE, L. L., *Proc. 2nd int. conf. intraut. contracept.* (The Excerpta Medica Foundation, Amsterdam), 1965.
102. SPEILBURGER, A. E. L. & OLEWINE, D. A., *Int. J. Fert.*, **11** (1966), 15.
103. HOK, T. T., WARSA, R., RAHIN, A., LSJAH, L., LOEN, L. K. & TIJAT, N. T., *Gebrutsch. Frauenheilk*, **26** (1966), 23.
104. MEYER, R., quoted by E. von Grafenburg, in *Rep. int. med. group for investigation of contracept., London*, 1930, 12.
105. KAR, A. B. & CHANDRA, H., *Indian J. exp. Biol.*, **3** (1965), 269.
106. KAR, A. B. & CHANDRA, H., *Am. J. Obstet. Gynec.*, **97** (1967), 279.
107. KAR, A. B., KAMBOJ, V. P., GOSWAMI, A. & CHOWDHURY, S. R., *J. Reprod. Fert.*, **9** (1965), 317.
108. KAR, A. B., KAMBOJ, V. P. & CHOWDHURY, A. R., *Curr. Sci.*, **35** (1966), 543.
109. ROY CHOWDHURY, R., MATHUR, V. S. & SAWHNEY, A. P., *Br. med. J.*, **1** (1967), 761.
110. KAR, A. B., *J. Fam. Welf.*, **13** (1966), 47.

Brain Gangliosides

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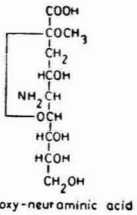
THE gangliosides were discovered some thirty years ago. While investigating some lipid storage diseases of the brain, the author obtained this new type of sphingolipids for the first time. Lipids are stored particularly in the ganglion cell but also to some extent in the glia cells. One of these diseases is the Niemann-Pick disease with excessive lipid deposition not only in nervous tissues but also in other organs. Another disease is infantile amaurotic idiocy, type Tay-Sachs, the lipid depositions in this case being limited to the nervous tissue. Sphingomyelin has been obtained as the predominant stored lipid in Niemann-Pick disease[7]. In Tay-Sachs disease, however, a hitherto unknown sugar containing lipid represents the accumulated substance[8,9]. This substance differs from cerebrosides in its water solubility, acidic properties, intensive purple colour formation with Bials orcinol reagent and the formation of appreciable amounts of humin substances on acid hydrolysis. Earlier[7], a lipid with the same properties was isolated from Niemann-Pick brains, though in smaller amounts. Similar lipids are also present in normal brain, although in smaller amounts. These compounds were given the name gangliosides by the author[10]. The characteristic behaviour which includes the typical Bial reaction and humin formation is due to the presence of neuraminic acid, which the author[11] isolated for the first time in 1941 as its well-characterized crystalline methoxy-glycoside.

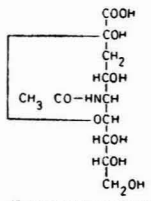
Subsequent studies showed that neuraminic acid is widely distributed in the animal kingdom. It is conjugated with many proteins, particularly in submaxillary mucins. Klenk and Lauenstein[12] were also able to obtain from this source a methylglycoside identical with that isolated from gangliosides.

Gangliosides as well as mucins contain the acetyl and sometimes the glycolyl derivatives of neuraminic acid. These acyl derivatives are often referred to as sialic acids. Ten years after the discovery of neuraminic acid this name was suggested by Blix *et al.*[13] for a substance obtained many years earlier by Blix[14] in trace amounts from submaxillary glands; he believed it to be a hexosamine containing disaccharide. But neither he nor others were able to prepare in the meantime this compound again, the nature of which was doubtful. The well-characterized N-acetyl-neuraminic acid was first obtained by Klenk and Faillard[15] and one year later by Blix *et al.*[16,17].

Neuraminic acid represents an amino acid closely related to the simple sugars. Work on structure elucidation, in which several laboratories[18-23] were involved, led to the conclusion that this acid represents a condensation product of pyruvic acid and mannosamine (I and II).



I Methoxy-neuraminic acid



II N-acetyl-neuraminic acid

Neuraminic acid was found to be a biologically interesting substance. It participates in several immunological reactions. Thus, Klenk and coworkers[24-28] could show, after Hirst, and Burnet and coworkers had done some pioneering work, that N-acetyl-neuraminic acid acts as the receptor site for influenza virus in virus haemagglutination. N-Acetyl-neuraminic is a component of surface mucoids of the erythrocytes. Influenza virus has an enzyme (receptor destroying enzyme, later named neuraminidase) which hydrolyses N-acetyl-neuraminic acid, leaving erythrocytes, which are no longer capable of agglutinating.

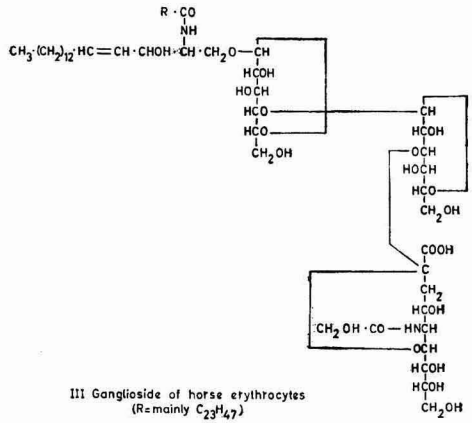
The human blood group substances M and N are also neuraminic acid containing mucoids. The enzymatic release of the N-acyl derivative abolishes their reactivity towards their antibodies[29-31]. According to Faillard and coworkers[32], the activity of the intrinsic factor required for the absorption of vitamin B_{12} depends on the presence of N-acetyl-neuraminic acid. Here again the activity is lost after enzymatic hydrolysis of N-acetyl-neuraminic acid.

Mainly three groups of workers have contributed in the recent 6-7 years to structure elucidation of gangliosides — Kuhn and coworkers in Heidelberg, Klenk and coworkers in Cologne and recently Mccluer and coworkers in USA. This task proved to be not very simple. The most interesting brain gangliosides are present as complex mixtures. Their separation into components was beset with several difficulties. After thin layer chromatography permitted easy identification of the different components, new perspectives for a successful solution of the problem were opened.

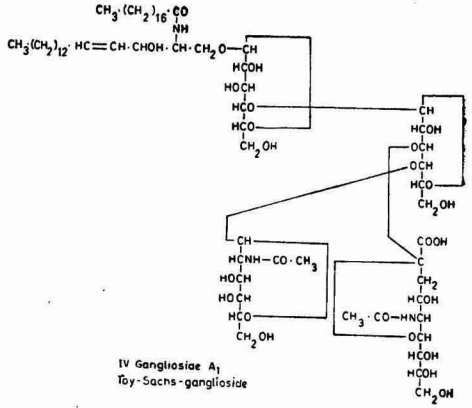
Gangliosides, with a very simple structure, are present in erythrocytes of several animals. They were isolated for the first time from horse erythrocytes by Yamakawa and Suzuki[33]. Structural studies by Padberg[2] and Klenk and Padberg[34] led to structure III.

Neuraminic acid can be easily cleaved off by mild acid hydrolysis, yielding N-glycolyl-neuraminic acid and a cerebroside with lactose instead of galactose. On hydrolysis using slightly stronger acid, galactose is released from this lactocerebroside yielding a glucocerebroside. The latter differs from brain cerebrosides in having glucose in place of galactose. It is remarkable that glucocerebrosides occur in

*With the cooperation of W. Gielen, K. Kener, G. Padberg, H. Wicha, W. Kunau, U. Liedtke, L. Hof and L. Georgias[1-6].



III Ganglioside of horse erythrocytes
(R=mainly $C_{23}H_{47}$)



IV Ganglioside A_1
Tay-Sachs-ganglioside

Morbus gaucher. This lipidosis is characterized by extensive depositions of this glucocerebroside in many organs, such as spleen and liver. Presumably, gangliosides are somehow involved in the metabolic disturbance of this lipidosis.

Further insight into the structure of gangliosides was obtained by periodate oxidation. Periodate cleaves C—C— bonds of compounds with vicinal hydroxyl groups. Periodate treatment of this ganglioside leads to the oxidation of a glucose moiety and of N-acetyl-neuraminic acid. Galactose which lacks a free glycol group is not attacked. Hydrolysis of the periodate treated ganglioside releases galactose but no glucose. The final proof for the mode of the linkages between the components was obtained on permethylation. On hydrolysis of the completely methylated ganglioside 3-methylsphingosine, 2,3,6-trimethylglucose and 2,4,6-trimethylgalactose were obtained.

A ganglioside with similar structure was isolated by Klenk and Heuer[35] from dog erythrocytes, but it was found to contain N-acetyl-NA instead of N-glycolyl-NA. The same ganglioside is also present in the ganglioside mixture of normal brain[36,37].

The structure of another ganglioside has been elucidated (IV). This ganglioside represents the main component of the gangliosides from brain in Tay-Sachs disease[38]. The ganglioside fraction isolated from Tay-Sachs brain differs from that of the normal brain in its rather homogeneous behaviour. This substance can also be obtained from the ganglioside fraction of the normal brain. It was the first brain ganglioside to be isolated in a fairly pure form[39,40]. Its structure differs from those of the gangliosides mentioned earlier in that position 4 of the galactose moiety is substituted by one N-acetyl-galactosamine molecule, forming the terminal sugar moiety. The structure has been derived from the following degradation studies: mild acid hydrolysis releases a glucocerebroside and an hexosamine containing disaccharide, the latter being composed of one molecule of galactose and one molecule of N-acetyl-galactosamine. Periodate oxidation of this ganglioside decomposes glucose and galactosamine. The only hexose released by hydrolysis is galactose. Finally, the permethylation method yields 2,3,6-trimethylglucose, 2,6-dimethylgalactose and 3,4,6-trimethylgalactosamine. The linkages of the substituents in positions 3 and 4 of galactose were not conclusively determined. Since the N-acetyl-neuraminic acid residue is linked to carbon atom 3 in a number of gangliosides from horse erythrocytes, it is safe to assume this mode of linkage also for the ganglioside in Tay-Sachs disease. Experimental evidence has been obtained recently by Ledeen and Salzman[41] for this.

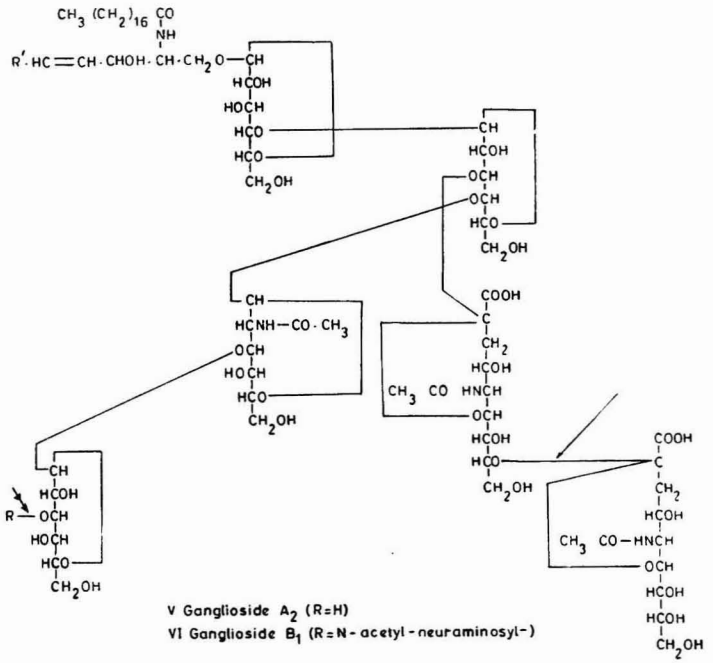
The two additional gangliosides representing the two major components of the ganglioside mixture from brain have structures V and VI. These structures have been elaborated by Klenk and coworkers[36,42]. These findings were shortly thereafter confirmed by the group in Heidelberg[43,44] in all essential details. One of the two gangliosides (A_2, V) differs from the Tay-Sachs ganglioside in having an additional galactose residue linked to C-3 of N-acetyl-galactosamine. In ganglioside B_1 (VI), a second N-acetyl-neuraminic acid molecule is ketosidically linked to C-3 of the terminal galactose. The carbohydrate moiety of this ganglioside contains two galactose molecules, each of which is substituted at C-3 by NANA.

Svennerholm and Raal[45] reported the occurrence of gangliosides with more than one NANA molecules and Kuhn and coworkers[46] that of gangliosides with glucose : galactose : galactosamine molar ratio 1 : 2 : 1.

Neuraminidase releases one of the two NANA residues of this ganglioside, the one marked by an arrow (linked to the terminal galactose). Thus ganglioside B_1 is transformed into A_2.

The structure of these two gangliosides has also been elucidated by hydrolysis studies. Mild acid hydrolysis releases besides the glucocerebroside, two disaccharides : N-acetyl-amino-galactosyl-galactose and β-D-galactosyl-1,3-(N-acetyl-)galactosamine[47]. The first one is obtained only in minute amounts, whereas the second disaccharide, a crystalline, well-characterized compound, is isolated in good yield. Here again periodate treatment of the ganglioside destroys the glucose molecule.

The mode of linkage between the components of the carbohydrate complex was determined by permethylation studies. Release of the two neuraminic



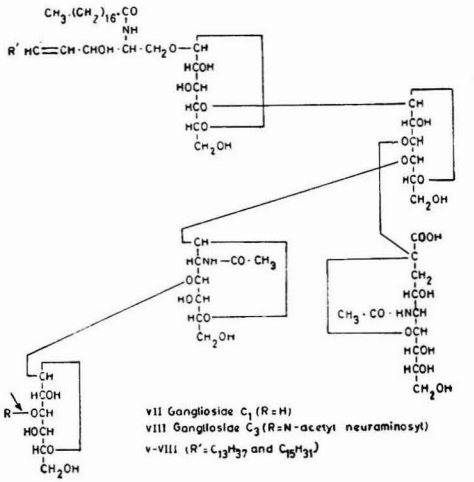
V Ganglioside A_2 (R=H)
VI Ganglioside B_1 (R=N-acetyl-neuraminosyl-)

acid molecules by mild acid hydrolysis yields the neuraminic acid-free glycolipid. The totally methylated substance yields the following products after acid hydrolysis: 2,3,6-trimethylglucose, 2,3,6-trimethylgalactose, 4,6-dimethylgalactosamine and 2,3,4,6-tetramethylgalactose. Therefore, the four hexose molecules are linked together in a linear arrangement to a tetrasaccharide with one of the two galactose molecules in terminal position.

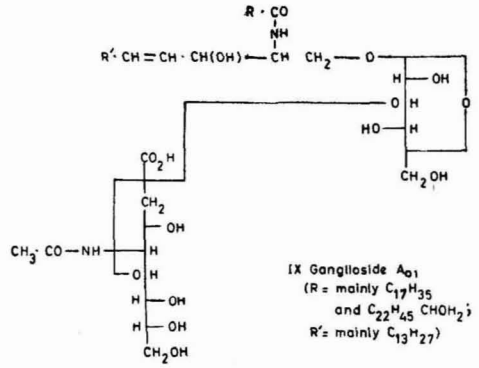
Among the products of hydrolysis of permethylated ganglioside A_2, 2,6-dimethylgalactose replaces 2,3,6-trimethylgalactose, the other methylated hexoses being the same as before. Thus, the neuraminic acid residue resistant to enzymatic hydrolysis is linked to position 3 of the central galactose. Finally, permethylated ganglioside B_1 yields the same methylated sugars as A_2, except that in place of tetramethylgalactose, the 2,4,6-trimethyl compound is present. Therefore, the N-acetyl-neuraminic acid residue, which can be hydrolysed enzymatically from ganglioside B_1, is linked to position 3 of the terminal galactose.

Ganglioside preparations obtained from normal brain also contain smaller amounts of other hexosamine containing gangliosides. Two of these were described by Kuhn and Wiegandt[43,44]. They proposed structures VII and VIII for these compounds. One contains two and the other three N-acetyl-neuraminic acid molecules. In both compounds two of three residues are linked to each other by a 2,8-ketosidic linkage. These two gangliosides have recently been isolated and investigated more closely[48]. The two compounds are transformed into ganglioside A_2 by the action of neuraminidase (ganglioside C_1 yielding one of the two and C_3 two of the three neuraminic acid residues). The loci of the fissions are indicated by arrows. The observations are in agreement with Kuhn's suggestion.

The structure was confirmed by permethylation. Ganglioside C_1 yielded the same methylated sugars as ganglioside A_2, C_3 the same as ganglioside B_1; ganglioside C_1 yields tetramethylgalactose, but ganglioside C_3 gives 2,4,6-trimethylgalactose. Periodate oxidation proved that in ganglioside C_1 the second N-acetyl-neuraminic acid molecule is linked to position 8 of the first; only the terminal molecule is degraded, the other being not attacked. Mild acid hydrolysis of this ganglioside during which products of hydrolysis leave the acidic medium by dialysis leads to the isolation of a



VII Ganglioside C_1 (R=H)
VIII Ganglioside C_3 (R=N-acetyl neuraminosyl)
V-VIII (R'=$C_{13}H_{37}$ and $C_{15}H_{31}$)



IX Ganglioside A_{01} (R = mainly $C_{17}H_{35}$ and $C_{22}H_{45}CHOH_2$; R' = mainly $C_{13}H_{27}$)

disaccharide consisting of two N-acetyl-neuraminic acid molecules, which can be easily hydrolysed enzymatically to free N-acetyl-neuraminic acid. With regard to the structure of ganglioside C_3, another possibility for the linkage of the two N-acetyl-neuraminic acid molecules exists, namely they are bound to the terminal and not to the central galactose residue.

To exclude this possibility, ganglioside C_3 was oxidized by mild periodate oxidation, which degraded the two terminal neuraminic acid residues. The glucose residue is not attacked because the free glycol groups have threo configuration. Periodate preferably attacks those with erythro configuration. This oxidation product was reduced with $NaBH_4$ and was prone to the neuraminidase action yielding ganglioside A_2.

Two of the other hexosamine containing gangliosides C_2 and C_4 have been isolated[48]. Both yield ganglioside A_2 after neuraminidase treatment. Ganglioside C_2 is an isomer of ganglioside C_3, containing three neuraminic acid molecules. It differs from ganglioside C_3 in that the terminal galactose is destroyed by periodate oxidation. Ganglioside C_4 probably contains 4 neuraminic acid residues, being linked in pairs to position 3 of the two galactose residues. Gangliosides C_2 and C_4 are present in very minute amounts. Due to their availability in minute amounts, their structures could not be determined.

Besides the glucose and hexosamine containing gangliosides discussed above, there are also brain gangliosides which contain galactose as the only sugar. Galactose is immediately attached to the sphingosine as in the case of brain cerebrosides. Klenk and Georgias[37] have recently isolated and examined a ganglioside, or rather a ganglioside fraction, with the structure IX.

Structure IX resembles the structure of an ordinary cerebroside with N-acetyl-neuraminic acid linked to position 3 of the galactose molecule; in other words, it is an N-acetyl-neuraminosyl-galactosyl-[N-acyl-] sphingosine. This is the simplest ganglioside known. A simple cerebroside can be easily obtained from this compound by the action of neuraminidase. The galactose moiety is not destroyed by periodate oxidation. Therefore, neuraminic acid must be attached to position 3 of the galactose residue. Also the methylated ganglioside releases 2,4,6-trimethylgalactose after hydrolysis, which confirms structure IX.

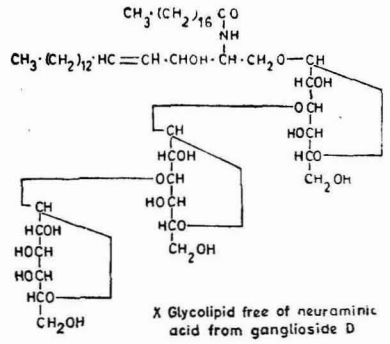
The similarity between this ganglioside and the brain cerebrosides is also evident from the fatty acid composition. It contains stearic acid and other higher homologues and in addition large amounts of α-hydroxy fatty acids of the cerebronic acid type. Moreover, the sphingosine fraction is almost exclusively represented by C_{18}-sphingosine, as in the case of cerebrosides. Most of the brain gangliosides contain a mixture of C_{18}- and C_{20}-sphingosines.

Although gangliosides of this kind are present in the brain in very small amounts, they might prove to be important in the process of myelin formation.

A compound containing three galactose and two NANA residues was also found and investigated by Klenk and Gielen[49] in detail. The action of neuraminidase produces a glycolipid with the structure X. Partial hydrolysis yields a β-galactosyl-galactose and galacto-cerebroside.

It is obvious that the gangliosides exhibit a wide variety of structures; particularly the hydrophilic groups may undergo variations. The hydrophobic group of the gangliosides, however, possesses astonishing simplicity. Thus, brain gangliosides usually contain only one fatty acid, namely stearic acid. In this respect, gangliosides differ from cerebrosides and sphingomyelin, both having the same hydrophilic group, namely phosphorylcholine and galactose respectively. The hydrophobic group varies considerably due to the larger number of fatty acid residues. It is probable that cerebrosides and sphingomyelins have functions in nervous tissue, which differ from those of the gangliosides. Cerebrosides and sphingomyelins are components of the myelin sheath, the gangliosides predominantly of the myelin-poor grey matter. It is likely that they are localized in some peculiar membrane structures of the ganglion cells.

There are indications that gangliosides are directly correlated to the nerve functions, more than any other sphingolipids. van Heyningen[50] and van Heyningen and Miller[51] showed that tetanus toxin binds specifically to gangliosides. McIlwain[52] postulated gangliosides being responsible for the electrical excitability of the nervous tissue. According to recent reports[53,54], gangliosides act as receptors for acetylcholine, which transfers the pulses from one



X Glycolipid free of neuraminic acid from ganglioside D

cell to the other. One of the gangliosides[55] has been assumed to be the receptor for serotonin. Finally, the lethal action of influenza virus during infection of the brain has been interpreted in such a manner that the receptor destroying enzyme neuraminidase alters the brain gangliosides in the same way as described earlier[56].

Summary

The isolation and structure elucidation of various brain gangliosides, including those containing more than one NANA or galactose molecule, have been reviewed. Gangliosides are found to be the predominant components of the myelin-poor grey matter and are presumed to be localized in some peculiar membrane structures of the ganglion cells. Their functions are shown to be more directly correlated to the nerve functions than any other sphingolipids.

References

1. GIELEN, W., *Über die Struktur der Ganglioside des Gehirns*, Doktordissertation, Köln, 1960.
2. PADBERG, G., *Über die hexosaminfreien Ganglioside aus dem Stroma von Pferderythrocyten*, Doktordissertation, Köln, 1961.
3. WICHA, H., *Zur Kenntnis der Ganglioside des Rindergehirns*, Doktordissertation, Köln, 1962.
4. KUNAU, W., *Über die Struktur von zwei hexosaminhaltigen Gangliosiden aus menschlichem Gehirn*, Doktordissertation, Köln, 1964.
5. HOF, L., *Über die Struktur von zwei hexosaminhaltigen Gangliosiden des menschlichem Gehirns*, Doktordissertation, Köln, 1965.
6. GEORGIAS, L., *Über die Einwirkung von Neuraminidase auf Ganglioside und über die Struktur von zwei hexosaminhaltigen Gangliosiden aus menschlichem Gehirn*, Doktordissertation, Köln, 1966.
7. KLENK, E., *Hoppe-Seyler's Z. physiol. Chem.*, **229** (1934), 151; **235** (1935), 24.
8. KLENK, E., *Hoppe-Seyler's Z. physiol. Chem.*, **262** (1939), 128; **267** (1940), 128.
9. KLENK, E., *Ber. dt. chem. Ges.*, **75** (1942), 1632.
10. KLENK, E., *Hoppe-Seyler's Z. physiol. Chem.*, **273** (1942), 76.
11. KLENK, E., *Hoppe-Seyler's Z. physiol. Chem.*, **268** (1941), 50.
12. KLENK, E. & LAUENSTEIN, K., *Hoppe-Seyler's Z. physiol. Chem.*, **291** (1952), 147.
13. BLIX, G., SVENNERHOLM, L. & WERNER, I., *Acta chem. scand.*, **6** (1952), 358.
14. BLIX, G., *Hoppe-Seyler's Z. physiol. Chem.*, **240** (1936), 43.
15. KLENK, E. & FAILLARD, H., *Hoppe-Seyler's Z. physiol. Chem.*, **298** (1954), 230.
16. BLIX, G., LINDBERG, E., ODIN, L. & WERNER, I., *Nature, Lond.*, **175** (1955), 340.
17. BLIX, G., LINDBERG, E., ODIN, L. & WERNER, I., *Acta Soc. Med. upsal.*, **61** (1956), 1.
18. KLENK, E., FAILLARD, H., WEYGAND, F. & SCHÖNE, H. H., *Hoppe-Seyler's Z. physiol. Chem.*, **304** (1956), 35.
19. KUHN, R. & BROSSMER, R., *Chem. Ber.*, **89** (1956), 2471.
20. GOTTSCHALK, A., *Nature, Lond.*, **176** (1955), 881.
21. CORNFORTH, I. W., DAINES, M. E. & GOTTSCHALK, A., *Proc. chem. Soc.*, (1957), 25.
22. COMB, D. G. & ROSEMAN, S., *J. Am. chem. Soc.*, **80** (1958), 497.
23. GIELEN, W., *Hoppe-Seyler's Z. physiol. Chem.*, **342** (1965), 170; **348** (1967), 329.
24. KLENK, E., FAILLARD, H. & LEMPFRID, H., *Hoppe-Seyler's Z. physiol. Chem.*, **301** (1955), 235.
25. FAILLARD, H., *Hoppe-Seyler's Z. physiol. Chem.*, **305** (1956), 145; **307** (1957), 62.
26. KLENK, E. & STOFFEL, W., *Hoppe-Seyler's Z. physiol. Chem.*, **303** (1956), 78.
27. KLENK, E. & LEMPFRID, H., *Hoppe-Seyler's Z. physiol. Chem.*, **307** (1957), 278.
28. KLENK, E. & UHLENBRUCK, G., *Hoppe-Seyler's Z. physiol. Chem.*, **311** (1958), 227; **312** (1958), 144.
29. SPRINGER, G. F. & ANSELL, N. I., *Klin. Wschr.*, **36** (1958), 442.
30. BARANOWSKI, T., LISOWSKA, E., MORAWIECKI, A., ROMANOWSKA, E. & STROUCKA, K., *Arch. human. terap. Doswiadczalney*, **7** (1959), 15.
31. KLENK, E. & UHLENBRUCK, G., *Hoppe-Seyler's Z. physiol. Chem.*, **319** (1960), 151.
32. FAILLARD, H., PRIBILLA, W. & POSTH, H. E., *Hoppe-Seyler's Z. physiol. Chem.*, **327** (1962), 100.
33. YAMAKAWA, T. & SUZUKI, S., *J. Biochem. (Tokyo)*, **38** (1951), 199.
34. KLENK, E. & PADBERG, G., *Hoppe-Seyler's Z. physiol. Chem.*, **327** (1962), 249.
35. KLENK, E. & HEUER, K., *Zentbl. Stoffwechs.-u. Verdau-Krankh.*, **20** (1960), 180.
36. KLENK, E. & GIELEN, W., *Hoppe-Seyler's Z. physiol. Chem.*, **330** (1963), 218.
37. KLENK, E. & GEORGIAS, L., *Hoppe-Seyler's Z. physiol. Chem.*, **348** (1967), 1261.
38. KLENK, E., LIEDTKE, U. & GIELEN, W., *Hoppe-Seyler's Z. physiol. Chem.*, **334** (1963), 186.
39. KLENK, E. & GIELEN, W., *Hoppe-Seyler's Z. physiol. Chem.*, **326** (1961), 158.
40. KLENK, E. & KUNAU, W., *Acta med. hung.*, **21** (1965), 405.
41. LEDEEN, R. & SALZMAN, K., *Biochemistry*, **4** (1965), 2225.
42. KLENK, E. & KUNAU, W., *Hoppe-Seyler's Z. physiol. Chem.*, **335** (1964), 275.
43. KUHN, R. & WIEGANDT, H., *Chem. Ber.*, **96** (1963), 866.
44. KUHN, R. & WIEGANDT, H., *Z. Naturf.*, **18b** (1963), 541.
45. SVENNERHOLM, L. & RAAL, A., *Biochim. biophys. Acta*, **53** (1961), 422.
46. KUHN, R., WIEGANDT, H. & EGGE, H., *Angew. Chem.*, **73** (1961), 580.
47. KLENK, E., HENDRICKS, U. W. & GIELEN, W., *Hoppe-Seyler's Z. physiol. Chem.*, **330** (1962), 140.
48. KLENK, E., HOF, L. & GEORGIAS, L., *Hoppe-Seyler's Z. physiol. Chem.*, **348** (1967), 149.
49. KLENK, E. & GIELEN, W., *Hoppe-Seyler's Z. physiol. Chem.*, **333** (1963), 162.
50. VAN HEYNINGEN, W. E., *J. gen. Microbiol.*, **20** (1959), 310.
51. VAN HEYNINGEN, W. E. & MILLER, P. A., *Hoppe-Seyler's Z. physiol. Chem.*, **24** (1961), 107.
52. MCILWAIN, H., *Biochem. J.*, **78** (1961), 24; **90** (1964), 442.
53. HOWARD, R. E. & BURTON, R. M., *Biochim. biophys. Acta*, **84** (1964), 435.
54. BURTON, R. M., HOWARD, R. E., BAER, S. & BALFOUR, Y. M., *Biochim. biophys. Acta*, **84** (1964), 441.
55. WOOLLEY, D. W. & GOMMI, B. W., *Proc. natn. Acad. Sci. U.S.A.*, **53** (1965), 959.
56. KELLY, R. T. & GREIFF, D., *Biochim. biophys. Acta*, **110** (1965), 548.

REVIEWS

THEORY OF LINEAR ACTIVE NETWORKS by E. S. Kun & R. A. Rohrer (Holden-Day Inc., San Francisco), 1967. Pp. xii+650. Price $ 19.25

Due to the advent of semiconductor devices and their applications in electrical engineering, the use of active networks in various forms has rapidly advanced during recent years. The study of the theory of linear active networks has, therefore, formed an integral part of the syllabus of courses in electrical engineering. There is, however, a pressing demand for suitable text-books on the subject for the undergraduate and postgraduate students in engineering. The present volume written by the competent authors is, therefore, a most timely gift to the students of engineering as well as to the practising design engineers. The thorough and exhaustive treatment of the subject by the authors in the twelve chapters of the book has made it equally valuable to the teachers dealing with these subjects.

Starting with clear definitions of the various features of n-port networks in the first chapter, the authors have established a strong background for the readers to closely follow the functional characteristics of such networks presented in the following chapters. The sixth chapter on scattering matrix, although brief, is adequate for following the analysis of coupled networks for single frequency and broad band behaviour included in the subsequent chapters. In the later chapters the authors have profitably dealt with the recently discovered active networks comprising tunnel diodes and parametric amplifiers, which cannot be ignored by any serious student of electrical engineering.

The last two chapters have been extensively devoted to the theory of single feedback amplifiers and multiple-loop feedback systems. The stability condition for such amplifiers has been derived on the basis of well-known Bode's design theory and Nyquist plots.

The authors have provided copious illustrations and problems at the end of every chapter along with a series of useful references of books and original papers including their own contributions and publications which are already known as standard works in the field of electrical engineering. The book is expected to be an indispensable companion of the present and future generations of the engineering graduates.

S. S. BANERJEE

PROGRESS IN REACTION KINETICS: Vol. 4, edited by G. Porter (Pergamon Press Ltd, London), 1967. Pp. vii+523. Price 100s.

This is the fourth volume of the series on *Progress in reaction kinetics.* It contains ten authoritative reviews on some new features of gas-phase reactions, photochemical reactions, proton-transfer reactions and electrode reactions.

There is emphasis on the quantitative reaction kinetics aspect in the first three reviews. The first review by Brocklehurst and Jennings deals with recent quantitative studies on reactions involving free nitrogen atoms. The next four reviews cover free radical reactions. Reliable kinetic data on the reactions of halogenomethyl radicals have been examined by Tedder and Walton in the second review. Radical-radical reactions, radical transfer reactions and radical addition reactions have been covered. Rate constants of reactions involving alkoxy radicals (RO) have been discussed by Gray, Shaw and Thyune. Heterolytic cleavage and consequent formation of carbonium ion is possible in the gas-phase reactions and this interesting aspect has been reviewed by Allan Maccoll and Thomas in the subsequent review. The next four reviews deal with one or the other aspect of photochemical reactions. Cundale and Davies have reviewed the primary processes in the gas-phase photochemistry of carbonyl compounds. The theoretical concepts for understanding the mechanism and rate of radiationless energy transfer have been described by Bennett and Kellog. Fluorescence lifetimes of aromatic molecules have been reviewed by Birks and Munro. Methods of measurement have been discussed and the experimental data for lifetimes in solutions and that for the crystal has been tabulated. Vassilév has emphasized three aspects of liquid-phase chemiluminescence in his review. Apart from the study of the phenomenon as such, use of chemical energy for obtaining excited molecules and the application of chemiluminescence as a means for studying the kinetics and mechanism of reactions has been discussed. Proton-transfer reactions are discussed by Albery in the next review which deals with interesting investigations to understand whether the proton is transferred via an H_2O bridge or not. The last review on chemical factors in electrode kinetics has been written by Conway.

The standard of each review is quite high. The reviews are timely. The volume would be useful for research workers in the field of chemical kinetics. Since the reviews are addressed to specialists, chemists in general cannot derive much benefit. However, the volume should find a place in libraries of universities and research institutes.

R. P. RASTOGI

ADVANCES IN HETEROCYCLIC CHEMISTRY: Vol. 7, edited by A. R. Katritzky & A. J. Boulton (Academic Press Inc., New York), 1966. Pp. xiv +511. Price $ 22.00

Volume 7 of *Advances in heterocyclic chemistry* contains seven chapters; three on general topics and four on specific groups of heterocyclic compounds. Katritzky and Boulton have compiled a most valuable bibliography of the literature on heterocyclic chemistry, arranged in a logical order based on ring size, the number, orientation and nature of the heteroatoms, and the degree of unsaturation. In addition, there is a list of general

sources and articles covering groups of natural and synthetic compounds.

The chapter on mass spectrometry by G. Spiteller will be of great assistance to workers on the structures of heterocyclic natural products. After a brief but clear account of basic principles, the fragmentation patterns of furans, pyrones, pyrans and sulphur-containing compounds are discussed. The mass spectra of alkaloids in particular are discussed in great detail, mainly because of the wide and successful application of mass spectrometry to alkaloids. Although there is a book on the subject by H. Budzikiewicz, C. Djerassi and D. H. Williams, the present account provides a very useful summary and supplement.

J. J. Eisch has discussed the preparation of halogen derivatives and the mechanistic aspects of the halogenation of heterocyclic compounds.

In the chapter on 1,2- and 1,3-dithiolium ions, H. Prinzbach and E. Futterer survey an area of very recent development.

G. Scheibe, whose work on the absorption spectra of cyanine dyes is well known, has written on diquinolylmethane and its analogues, jointly with E. Daltrozzo. Following a brief account of synthetic methods, the chapter deals with tautomerism and reactions at the methylene carbon and nitrogen atoms.

A. Hetzheim and K. Möckel have reviewed recent advances in 1,3,4-oxadiazole chemistry. The section on uses is specially valuable; it is highly condensed, but reviews all patents and scientific literature on 1,3,4-oxadiazoles in the synthesis of drugs, dyes, polymers, etc.

P. Bosshard and C. H. Eugster survey the development of the chemistry of furans from 1952 to 1963, of great interest to workers on natural products because of the wide occurrence of the furan ring system. The chapter, which has over 450 references, concludes with a list of naturally occurring furans.

K.V.

ADVANCES IN HETEROCYCLIC CHEMISTRY: Vol. 8, edited by A. R. Katritzky & A. J. Boulton (Academic Press Inc., New York), 1967. Pp. xiv +404. Price $ 19.00

Volume 8 has been produced more quickly than the earlier volumes and the literature has been covered through early 1966. For some reason not easy to understand, Volumes 7 and 8 have no subject index. A notable feature is that ten of the fifteen authors are from Eastern Europe and one is from India; another is that there are many references to Indian workers. Four of the eight chapters deal with specific groups of compounds, and the others with general reactions.

J. M. Tedder, whose method for the direct introduction of the diazonium group into phenols, phenolic ethers and tertiary aromatic amines is a major advance in the chemistry of azo compounds, has discussed the preparation and properties of heterocyclic diazo compounds. Their light-sensitive properties have been used in recent years for two different photoreproduction processes, and the last section outlines the relevant patents.

J. Pliml and M. Prystas have described the scope and limitations of the reaction of 2,4-dialkoxypyrimidines with halogenoses (the Hilbert-Johnson or Hilbert-Rist reaction) and have compared it with other methods for the synthesis of nucleosides and their derivatives. They conclude that it is a suitable complementary method.

In a short chapter of 20 pages, B. S. Thyagarajan gives a very clear account of Claisen rearrangements in nitrogen heterocyclic systems.

Reiche's important work on cyclic peroxides and related reactions are discussed by two of his collaborators (M. Schulz and K. Kirschke). Since ozonides and photo-oxides belong to this class, a review of their chemistry is of wide general interest.

Except for a review in an inaccessible Polish journal, F. D. Popp and A. C. Noble have written the first review of the diazepines, a heterocyclic group which has excited great interest because of the discovery of librium (chlordiazepoxide). The fantastic sale value of this tranquillizer has stimulated intensive research on alternate synthetic methods and the preparation of analogues. The chapter contains 330 references and gives a comprehensive account of most of the known diazepines at some sacrifice of readability; a fuller discussion of the mechanism of the reactions, some of which involve novel rearrangements, leading to the medicinally important diazepines, and a discussion of the relation between structure and pharmacological properties would have been welcome.

M. Ionescu and H. Mantsch have reviewed recent advances in the chemistry of phenoxazines. Dyes of this class are among the oldest synthetic dyes, but the renewed interest because of the discovery of many naturally occurring and biologically active phenoxazines justifies the inclusion of this chapter, which gives an excellent summary of our present knowledge of preparative methods and properties.

Monocyclic sulphur-containing pyrones (thiapyrones) are reviewed by R. Mayer, W. Broy and R. Zahradnik. Most of the compounds, listed in six tables, were synthesized recently. An account of the synthetic methods is followed by a stimulating discussion of physical properties and chemical reactivity against a background of quantum chemical calculations.

K. H. Wunsch and A. J. Boulton have reviewed indoxazenes and anthranils, benzo derivatives of isoxazoles. The known compounds are listed in 18 tables, and the chapter is invaluable for reference purposes.

K.V.

PROBLÈMES ACTUELS DE BIOCHIMIE APPLIQUÉE: Vol. 1, edited by M. L. Girard (Masson et Cie, Publishers, Paris), 1967. Pp. vi+368. Price 90 fr.

The present series is an attempt to bridge two disciplines — clinical medicine, with its patients and problems of diagnosis, and biochemistry, which is every day offering new possibilities for diagnosis and follow-up of clinical conditions.

Volume 1 of the series contains seven review articles. The subjects are: (i) Exchange of gases in lungs and in cells and its role in the maintenance of acid-base equilibrium; (ii) Estimation of ammonium

ion and its applications in biology and medicine; (iii) Serotonine; (iv) Paper electrophoresis; (v) Metabolic errors of carbohydrate metabolism — analytical problems in their study; (vi) Biochemistry and immunochemistry of myelomas and paraproteinemias; and (vii) Problems of dehydration in the infant. They have been written by people actually engaged in the area, who are conversant with both the clinical aspect as well as with laboratory investigations. Each review summarizes, in the first instance, the basic academic background of that topic and later gives, in great detail, the methods used in clinical investigation and their interpretations. The diagnostic value of a test is evaluated statistically on the basis of patients examined by the authors. Useful inclusions in the text are the difficulties and slips encountered in the standardization of a method. These details render the book particularly beneficial for practical work in a clinical laboratory.

The treatment of subjects in the different reviews would be evident from a typical example. The review on myelomas and paraproteinemias, written by F. Rousselet, gives first the definitions of terms, then the current notions on the structure of immunoglobulins and their classification, which, incidentally, has been done in a remarkably clear manner without any sacrifice of precision or accuracy of facts. Then follows a section on the variety of biochemical tests which can be employed for the diagnosis of myelomas. The degree of dependability of each test with its upper and lower limits has been mentioned on the basis of 111 cases seen by the author himself, besides the deductions permissible from two other series of cases examined by other investigators. The methods of choice are then mentioned in full detail with precautions and counter-indications. The author gives the commercial source of reference antisera, but also describes the procedures employed by his laboratory to prepare the same in view of the high cost of the antisera from commercial sources. After detailing the procedures and techniques, the author gives the findings in a number of typical cases illustrated with the immunoelectrophoretic patterns of the patient's sera. Finally the author discusses situations where a test may be indicative, while the disease is not yet apparent (latent period or non-specific manifestations) and also the rare situations where the clinical condition is present without the abnormal results of biochemical and immunochemical tests.

The book is essentially of a practical nature and that is where the principal value as well as the limitation of this treatise lie. The book is in French and it is adequately illustrated with figures and data. It should be useful to most clinicians, pathologists and biochemists in medical colleges and hospitals and should, in any case, be a part of libraries of all medical colleges and hospitals.

G. P. TALWAR

PROCESSING OF POLYESTER-COTTON BLENDS by G. G. Kulkarni & S. S. Trivedi (Ahmedabad Textile Industry's Research Association, Ahmedabad), 1967. Pp. 151. Price $ 6.00 or Rs 27.00

Kulkarni and Trivedi's book, *Processing of polyester-cotton blends*, has a nice get-up and the printing is good. The whole approach to the writing of the book appears to have been conceived on sound lines. The authors need to be congratulated.

Chapter I deals with the properties of fibres and fibre blends. Various tables provided in this chapter are useful, though the authors could have included the original sources of references in these tables. Also, the description of the quantitative chemical analysis of mixtures of polyester fibres with cotton is too scanty and is not sufficiently authoritative.

Chapter II deals with sizing; the approach and general principles of sizing have been well covered. The authors explain in the preface that the book has been written with a view to bringing together their own experience in Ahmedabad mills. However, beyond well-known generalizations, there does not seem to be any specific reference to local experience.

Chapter III deals with bleaching and finishing and the authors must be commended for the excellent treatise given to the subject of heat setting. The mill technologist will find this chapter of particular value. There is also a useful treatise on pilling but, unfortunately, modern trends in researches in this subject are not properly covered. Durable press finishing, finishing for antistatic effects and the new Du Pont CHC process for improving visual and tactile properties of blended fabrics have also been discussed. It is obvious, however, that the authors have a very limited experience in these fields.

Chapter IV deals with dyeing. The broad generalized aspects of fibre plasticization and high temperature dyeing have been covered adequately. Here again, one would have liked the authors to be more specific about Indian experiences, the types of equipment available in India and general guidelines to the technologists who are called upon to work in the Indian setting.

Chapter V deals with printing and one is happy to note the authoritative trend in the description of various printing steps and the recommendations made.

The book will be found useful for students and technologists on the floor-shop. To the researcher, it is a useful starting point.

V. B. CHIPALKATTI

MODERN FOUNDATION METHODS by Rolt Hammond (Oxford & IBH Publishing Co., Calcutta), 1967. Pp. viii+176. Price 52*s*.

This book on *Modern foundation methods* is off the beaten track. Most recent publications on foundation engineering tend to deal almost exclusively with theoretical soil mechanics and laboratory tests on soils. Practical applications and the problems encountered in the field do not receive the attention that they deserve. In their effort to idealize soil behaviour, most authors overlook to emphasize that foundation engineering is as much an art as a science.

This book with its pronounced practical bias ought to act as a corrective to this attitude. It deals with various techniques employed in modern foundation practice and the features of each technique are clearly explained by means of illustrations drawn from actual practice. The principles of soil

mechanics and the need for scientific soil exploration are stressed in the beginning. The second chapter deals with grouting techniques. The colcrete and prepakt processes are discussed in some detail. There are four chapters devoted to pile foundations. These discuss driven, cast in-place large-diameter bored piles and vibratory methods of piling. A complete chapter is devoted to vibration-controlled machine foundation. Case histories are given. The concluding chapter discusses special foundation problems. The practising engineer and the consultant will find the book to be of absorbing interest.

G. S. RAMASWAMY

COMPLETENESS OF SCIENCE by Richard Schlegel (Appleton-Century-Crofts Inc., New York), 1967. Pp. xi+280

Like some of the Indian Upanishads dealing with the qualities of the *atman*, the author, a Professor of Physics at the Michigan State University, discusses the question whether physical sciences possess the quality of completeness. Although he has not come to any definite conclusion, the discussions are profound and illuminating. The various relevant thoughts expressed in the past, by creative and scholarly scientists, have been critically reviewed and commented upon.

The book is divided into fourteen chapters. Chapters 6-12 respectively deal with concepts of infinity, cosmology, decisions in cosmology, the natural limits of description, the observer in quantum physics, criticisms of quantum theory and the atomic finitude in nature. These are well-written 'status reports' on the corresponding aspects of mathematical and physical sciences. Chapter 1 is an introductory chapter enunciating the problems. Five of the other chapters are on: a philosophy of science, complete description in science, completeness and limitations of science, completeness and explanation, and the Gödel incompleteness theorem. They deal with the philosophy of science and the undecidability of mathematical logic. The last chapter on the non-cognitive completion of science deals with the relation between the humanities, art, religion and sociology with the physical sciences.

Science is a description of the universe as man experiences it and its understanding through appropriate counterparts in physical theory as conceived by the human mind, and to that extent there is an inherent incompleteness in science. In addition to this factor, there are limitations imposed on science through logical and mathematical undecidability and through the uncertainties characteristic of the quantum and the cosmological theories.

The book provides a thought-provoking reading for one with a good background of education in science and with an interest in the philosophy of science apart from its utilitarian aspects. The printing and get-up are good, although the reviewer would welcome the use of a larger and sharper type.

P. R. PISHAROTY

PUBLICATIONS RECEIVED

INTRODUCTION TO FORTRAN PROGRAMMING by M. N. Keshava Rao (Nem Chand & Bros, Roorkee, India), 1967. Pp. xi+224. Price Rs 11.25

VÝSLEDKY BÁŇSKÉHO VYZKUMU Č.5 (Hornický Ústav Csaw, Praha 8-Liben), 1966. Pp. 237

ADVANCES IN ENZYME REGULATION edited by George Weber (Pergamon Press Ltd, London), 1966. Pp. xiv+381. Price $ 15 or 105s.

STATIC ELECTRIFICATION: 1967 CONFERENCE PROCEEDINGS edited by A. C. Stickland (Institute of Physics & Physical Society, London), 1967. Pp. vi+173. Price £ 10

A SYMPOSIUM ON CHEMICAL ADDITIVES IN FOOD edited by R. W. L. Goodwin (J. & A. Churchill Ltd, London), 1967. Pp. viii+128. Price 20s.

TRANSITION METAL INTERMEDIATES IN ORGANIC SYNTHESIS by C. W. Bird (Logos Press Ltd, London), 1967. Pp. vii+280. Price $ 13.00

NOTES & NEWS

Rainbow laser

Scientists of the International Business Machines Corporation have developed a simple liquid laser which can produce a 'rainbow' of different colours. So far, green, yellow, orange and red laser lights have been produced, and in principle it should be possible to produce all wavelengths in the visible and infrared spectrum. The colour of the beam is changed simply by refilling the liquid laser with different solutions of organic dyes.

Last year IBM scientists Peter P. Sorokin and J. R. Lankard observed the first lasing action in an organic dye — chloro-aluminium phthalocyanine. This discovery presaged lasing in other organic dyes and a filling of the visible spectrum with laser light. However, the initial discovery was considered somewhat academic because the organic dye had to be pumped by a giant-pulse ruby laser. This is a cumbersome and expensive pumping method, and no wavelengths shorter than the ruby's can be produced unless complex frequency-doubling techniques are used.

In their studies, Sorokin and Lankard found that fast pumping is a necessary condition for lasing in fluorescent dyes. On the basis of this finding they developed an extremely fast flash lamp and laser assembly which can meet this stringent requirement. It generates pumping pulses with a risetime of 300 nanoseconds compared to hundreds of microseconds for the conventional flash lamps. As a result, it is now possible to produce lasing action in many of the different coloured organic dyes easily,

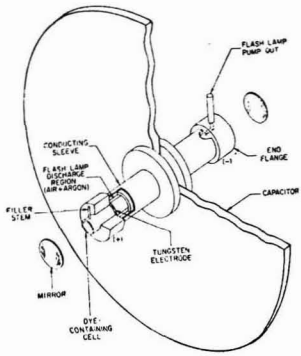


Fig. 1 — The experimental rainbow laser

because of the wide spectrum of the flash lamp.

Already four fluorescent organic dyes of the xanthene family have been pumped successfully, producing green, yellow, orange and red laser lights (Table 1). It should be possible to achieve lasing action across the entire visible spectrum with other fluorescent dyes using the new flash lamp. In addition, the emission band of any one dye can be 'shifted' by at least 600 A. by changing the concentration of the dye.

The search for lasing action in the many hundreds of untested organic fluorescent dyes will be speeded by the IBM finding on the risetime requirements of the pumping pulse. In most organic dyes, the energy in the excited singlet state 'leaks away' very quickly into a non-lasing triplet state. If the risetime of the pumping pulse is long, many of the atoms already in the excited singlet state will be converted to the non-lasing triplet state. Once in this state, they can absorb great amounts of energy at the laser wavelength. The IBM scientists found that the population build-up in the excited singlet state must be achieved very quickly before this secondary process takes over. They have described this requirement in mathematical terms, which can be used to determine the needed risetime to achieve lasing in a particular dye.

The new flash lamp and laser assembly (Fig. 1) consists of three basic elements: (i) the active laser cell, (ii) surrounding flash lamp, and (iii) a discharge capacitor. The laser cell is a quartz tube with polished ends, which contains the organic dye in a suitable solvent. This is surrounded by a second quartz cylinder; a thin space between the cylinders constitutes the flash lamp discharge region. Ring electrodes are placed at opposite ends of the annulus and the discharge takes place between the electrodes in an air-argon mixture.

A capacitor disc is placed coaxially over both the cylinders, and conducting paths to the end electrodes are made with copper sleeves over the outer quartz cylinder. This arrangement lowers the lamp inductance, which is a prime consideration in reducing the risetime of the pumping pulse.

The new flash lamp-pumped lasers emit in a broad band about 100 A. wide at varying frequencies. In all cases, the band can be shifted to the longer wavelengths by increasing the dye concentration. Because of the fairly wide band, there exists the possibility that the new lasers could be operated in a phase-locked mode to produce extremely short bursts of laser light.

TABLE 1 — CHARACTERISTICS OF FLASH-PUMPED ORGANIC LASERS*

Dye	Solvent	Colour and wavelength of laser beam
Acridine red	Ethyl alcohol	Orange (6015 A.)
Rhodamine 6G	Ethyl alcohol	Yellow (5850 A.)
	Water	Orange
	Heavy water	Orange
Rhodamine B	Ethyl alcohol	Red
Na fluorescein	Ethyl alcohol	Green (5500 A.)
Na fluorescein	Water	Green
Na fluorescein	Heavy water	Green

*600 A. shift in emission band as concentration is increased from 10^{-5} to 10^{-3} molar.

Luminescence of alkaline-earth pyrophosphates

Alkaline-earth pyrophosphates when activated with divalent europium become very efficient

phosphors, emitting deep blue or ultraviolet light. In contrast to the more common red and orange emitting Eu^{3+} phosphors whose emission spectrum consists of lines, the emission spectrum of Eu^{2+} phosphors comprises bands.

Calcium and strontium, activated by Eu^{2+}, yield very efficient phosphors, but the partial substitution of Ca or Sr by Ba leads to a gradual decrease of brightness, no luminescence being found at about 60 atom per cent substitution. The reason is an initial expansion of the lattice due to the incorporation of Ba as shown by X-ray analysis.

The quenching temperature (i.e. the temperature at which the brightness decreases to 50 per cent of its value measured at room temperature) lies between 125° and 200°C. This temperature is much lower than that for most Eu^{3+} activated phosphors.

The Eu^{2+} activated phosphors are very suitable for application in lamps (both low and high pressure mercury vapour types) for photocopying. A definite advantage is that the peak intensities of the Eu^{2+} activated phosphors are such that their whole emission spectrum falls within the range of the maximum sensitivity of the available photocopying papers. Consequently, these phosphors make a higher printing speed possible [*Philips Res. Repts*, **22** (1967), 355].

Photosynthesis of nitrosoformaldehyde

The transient spectrum in the region 2000-2100 A. consisting of diffuse bands with centres at 2070, 2043, 2023(?), 2000 and 1982 A., observed during the flash photolysis of methyl nitrite and previously thought to be that of methoxyl [McGrath, W. D. & McGarvey, J. J., *Nature, Lond.*, **201** (1964), 991; *Trans. Faraday Soc.*, **60** (1964), 2196] has been attributed to nitrosoformaldehyde [Napier, I. M. & Norrish, R. G. W., *Proc. R. Soc.*, **299** (1967), 337].

The spectrum was produced by flashing formaldehyde, acetaldehyde, methyl formate or glyoxol in the presence of nitric oxide and excess of nitrogen as coolant. None of these compounds could give the spectrum in the absence of nitric oxide. The spectrum given by methyl nitrite-nitrogen mixture was much more intense when nitric oxide was added to the mixture. The spectrum was not observed when likely sources of methoxyl, such as dimethyl sulphate, dimethyl sulphite or dimethyl carbonate, were flashed under isothermal conditions. It was inferred that methoxyl could not be the carrier responsible for the spectrum. Moreover, the half-life of the carrier (100 msec.) is unusually long for a small radical like methoxyl, but is more consistent with a triplet or a very reactive singlet. Nitric oxide is an essential reactant in any system for the spectrum to be obtained, and is one of the radicals taking part in a radical-radical reaction; the other radical is most probably a formyl, leading to the formation of nitrosoformaldehyde.

With methyl nitrite, the origin of formyl radical can be explained by the following scheme of reactions:

$$CH_3ONO \xrightarrow{h\nu} CH_3O + NO$$
$$2CH_3O \longrightarrow CH_2O + CH_3OH$$
$$CH_3 + CH_2O \longrightarrow CH_3OH + CHO$$

Reduction of cyano- and nitropyridines with sodium borohydride

Pyridine derivatives, with electrophilic substituents, like cyano and nitro groups in 2 or 4 positions, have been reduced by sodium borohydride. This appears to be the first example of the reduction of common cyano group by sodium borohydride to the corresponding amine. 2- or 4-cyanopyridine and 2- or 4-nitropyridine (0·01 mole) have been reduced by refluxing (for 5 hr in the case of cyano compounds and 1 hr in the case of nitro compounds) with sodium borohydride in ethanol (30 ml.). Molar ratios of 5:1 and 3:1 for borohydride : pyridines have been employed for cyano and nitro compounds respectively. Yields of the order of 50 per cent and more are reported. Since the cyano and nitro benzenes are not reduced under identical conditions, it is suggested that the resonance effect of the pyridine ring renders the 2 and 4 positions somewhat positive and the hydride attack on the substituents is enhanced by this inductive effect [*Chemy Ind.*, (1967), 1325].

National Geophysical Research Institute, Hyderabad

The annual report of the Institute for the year 1966 presents the main research activities of its eight research groups dealing with seismology, gravity and isostasy, geomagnetism and geoelectricity, rock mechanics, palaeomagnetism and heat flow, theoretical geophysics, geophysical prospecting, and geophysical instrumentation.

Work on the establishment of the seismological observatory, initiated in 1965, was almost completed. The magnetic observatory, established in 1964, continued recording geomagnetic elements. A geoelectric observatory for studies on the rapid variations of earth's electromagnetic field has been established at Choutuppal near Hyderabad. Gravity data from various organizations, such as the Geological Survey of India (GSI) and the Oil & Natural Gas Commission (ONGC), were obtained and reduced to a common datum for standardization. Gravity surveys were carried out in the peninsular shield for studying the crustal structure and probable relationship of gravity anomalies to mineralized regions. The construction of a chamber for hydrostatic pressures up to 5 k bars was started to study the elastic properties of rocks under high pressures.

The results of palaeomagnetic studies for Jurassic to Eocene rocks have indicated that the Indian sub-continent has drifted from southern latitudes of 46° (for Nagpur) about 130 million years ago to about 9° north 30 million years ago, corresponding to an average approximate rate of 6 cm. per year.

Heat flow measurements were made in a number of regions including Kolar goldfields. Temperature gradients in oil wells in Assam and in other parts of the country were obtained from Oil India Ltd and ONGC. Measurements were also made by the Institute staff in some of these areas.

A rigorous theoretical study on electromagnetic induction processes in a double sphere has revealed that under certain favourable circumstances the inner sphere shows itself better in the presence

of a conducting cover than in its absence. This phenomenon of 'negative screening' marks an important contribution to the study of electromagnetism in general and to induction prospecting in particular. A theoretical possibility was established which provides a basis for simulating conductors of directional inhomogeneity by means of spatial deformations in the electromagnetic model experiments.

The study of nonlinear transparency of pulse forms has revealed that even under perfectly elastic conditions the seismic pulse shapes get deformed in a manner depending predominantly upon the velocity variations in the media they traverse. Study of Love wave propagation in an anisotropic, inhomogeneous layered structure has yielded results of great value in delineating the finer structural details of the earth as well as in seismic prospecting where deep-layered structures are considered.

The geophysical prospecting group conducted gravity, magnetic, resistivity, electromagnetic and other geophysical surveys for government and private agencies and attempted the development of new methods of field operation and interpretation. Geophysical surveys for chromite deposits in Sukinda (Orissa) and for copper in Ingildhal (Mysore) and Khetri belt (Rajasthan) were carried out. Magnetic surveys for iron ores in the Kudremukha region (Mysore) were undertaken for the National Mineral Development Corporation. Geophysical surveys for ground water were undertaken in certain areas of Andhra Pradesh. Considerable amount of work was done in extending the method of continuation to interpret gravity, magnetic, electrical and electromagnetic data. Convergence conditions for various simple geometries, usually encountered in ore prospecting, were worked out. A Hammer type shallow refraction seismograph has been constructed with indigenous know-how and components.

Integrated geophysical projects both in the field and laboratory were undertaken as part of the Upper Mantle Project to accumulate data for studying some outstanding geophysical problems. Detailed investigations of the physical properties of rocks were continued in parts of the Cuddapah basin, Dharwar belt, Aravalli belt and the Singhbhum region.

Central Building Research Institute, Roorkee

The research work carried out by the Institute during the year 1966 has been primarily concerned with building materials; soil engineering; efficiency of buildings; building processes, plants and productivity; and architecture.

Considerable improvement has been made in the design of the indigenous extrusion machine for brick making. The construction of an archless brick kiln, designed in the Institute, was completed. This kiln is divided into 20 chambers, the chamber capacity being about 7000 bricks. Attempts were made to substitute magnesite by dolomite for the manufacture of oxychloride cements. A process has been developed for curing asbestos sheets and pipes for improving their strength. The process was tried in an asbestos cement factory on pipes made from imported crysotile and those made from mixtures of crysotile and the indigenously available amphibole in various proportions up to 60 per cent of the latter. The bursting pressure of pipes cured by the Institute process was found to be well above the Indian Standards Specifications.

Two corrosion inhibiting pigments were prepared from indigenous raw materials with a view to replacing the imported red lead. Three formulations of waterproofers were developed from sodium silicate to replace the costlier silicone preparations available in the market. Work on building lime carried out comprised studies on magnesian and dolomitic limestones and preparation of calcium hydroxide crystals.

Several improvements have been made in the techniques of laying under-reamed pile foundations and the process is now being widely adopted by both public and private organizations. It has resulted in savings of about 60 per cent in foundation costs. The improved technique of soil exploration and sampling using bentonite mud was successfully adopted up to a depth of 80 m. for site investigation for a bridge foundation. Reliable methods for *in situ* determination of the bearing capacity of boulder deposits have been developed.

An apparatus has been developed for rapid determination of the thermal conductivity and diffusivity values of building and insulating materials. Studies on solar illumination and equations developed representing sky components have led to the facility of pre-estimating the availability of sky illumination at an indoor point due to a given window at the design time. Based on this, simplified design data for choosing the most appropriate window sizes have been obtained. Sound insulation of partition walls; effect of driving rain on the durability and functional efficiency of buildings; and ventilation in multistoreyed constructions were some of the other investigations pursued.

Investigations were carried out on the design of load bearing brick work for multistoreyed buildings; the designs proposed have been accepted in principle by the Indian Standards Institution. Programmes based on CPM and PERT techniques were developed for several construction projects and they helped in increasing the efficiency of planning and subsequent construction. Successful trials were made on the single stack system of plumbing up to four-storey buildings.

Studies on the use-efficiency of space in five-class primary schools were undertaken with the aim of achieving economy in space. Experiments with three-class rooms in a number of schools led to about 40 per cent economy in space requirements. Under an urban land development project, investigations were carried out regarding length of road, open space per dwelling, land coverage, population density and area under roads. A work study survey was conducted on the placement, size and internal layout of kitchens in buildings.

Physics of the Earth and Planetary Interiors

This new journal, devoted to papers dealing with the application of the physical sciences to the study of the earth's crust, mantle and core and to the interiors of the

planets, is being published by North-Holland Publishing Co., Amsterdam, since July 1967. The character of the journal is interdisciplinary with coverage of physics, chemistry, geology, astronomy and mathematics. The journal is published bimonthly, the annual contribution being £ 9 or $ 25.00.

Announcements

▪ *The Twelfth International Symposium on Combustion* will be held during 14-20 July 1968, at the University of Poitiers, France (approximately 200 miles south of Paris). The organizers are the University of Poitiers and the French section of the Combustion Institute.

The technical programme will include sessions for contributed papers and six colloquia on: (i) Combustion instability (instability in liquid propellant rocket systems, solid propellant rocket systems, and industrial burners); (ii) Detonation, both condensed phase and gas phase (low velocity waves, failure mechanisms, transition to detonation, and complex detonation structure); (iii) Supersonic combustion (effects of fuel injection, mixing, ignition and reaction kinetics, interaction of combustion processes with flow phenomena and geometrical constraints); (iv) Chemical kinetics in flames (elementary reactions of oxygen atoms, pyrolytic reactions of importance in combustion and flames, chemi-ionization, shock reactions, and general topics); (v) Radiation from practical flames (furnace, and gas turbine and rocket flames); and (vi) Combustion problems related to air pollution (mechanism for incomplete combustion, particulate formation, nitrogen oxide formation, and methods for control).

Sessions on the following topics are likely to be held if a sufficient number of contributions are received: Ignition and combustion of fuels and propellants; Decomposition of unstable substances; Flame mechanisms and structure; Chemical syntheses in flames; Mass fires; Engine combustion; and Numerical computation studies of reactive flow.

Abstracts (in quadruplicate) of papers intended for presentation, 800-1200 words in length, should be sent to the Combustion Institute, 986 Union Trust Building, Pittsburgh, Pennsylvania 15219, USA.

▪ *Symposium on Electromagnetic Waves* — This symposium will be held at Stresa, Italy, during 3-8 June 1968. Papers would be presented on (i) Propagation in inhomogeneous or anisotropic media, (ii) Propagation in random media, (iii) Very low frequency propagation, (iv) Nonlinear phenomena in wave propagation, (v) Antennas, and (vi) Application of computers for solving electromagnetic problems. Summaries of papers (800-1600 words) may be sent to G. P. Bava, Secretary of the Organizing Committee, c/o Instituto di Elettronica e Telecomunicazioni, Politecnico, C. so Duca degli Abruzzi, 24, 10129 Torino, Italy.

▪ *Fourth World Congress on Fertility and Sterility* — This congress will be held at Tel Aviv, Israel, during 20-27 May 1968. The subjects to be covered in the congress are: Immunological aspects of reproduction; Neurological and psychological factors of infertility; Eugenic, genetic and para-genetic factors influencing reproduction and development of foetus; Effects of prolonged use of oral and intrauterine contraception on fertility; Genital tuberculosis in infertility; Seminal fluid and accessory glands in infertility; New methods of diagnosis and treatment of sterility and infertility. Further information regarding the congress may be obtained from Secretary General, IV Congress on Fertility and Sterility, P.O.B. 26102, Tel Aviv (Israel).

▪ *World Conference on Earthquake Engineering* — The International Association of Earthquake Engineering will hold the fourth world conference on earthquake engineering in Santiago, Chile, during January 1969. The topics of discussion will be: Observation in recent earthquakes; Seismicity and ground motion; Construction materials and elements; Response of structures; Design of small buildings; Soils and soil structures; Design of large buildings; Foundation and soil structure interaction; Design of other structures; Design criteria; Construction practices; Research programmes; and Repair and strengthening structures. One-page abstract of papers intended to be presented at the conference may be sent to Prof. Grahm H. Powell, Secretary of the Technical Committee, Fourth World Conference on Earthquake Engineering, 416 Mclaughlin Hall, University of California, Berkeley, California 94720, USA.

▪ *Directory of Indian Behavioural Scientists* —The Behavioural Sciences Centre, which is compiling this directory, has invited the behavioural scientists in India to provide information regarding their placements, addresses, etc., for inclusion in the directory. The details should be sent to Dr J. M. Ojha, Behavioural Sciences Centre, 32 Netaji Subhas Marg, Delhi 6. Institutions may also send details regarding their staff associated with or engaged in research in psychology, education, sociology, anthropology and community development.

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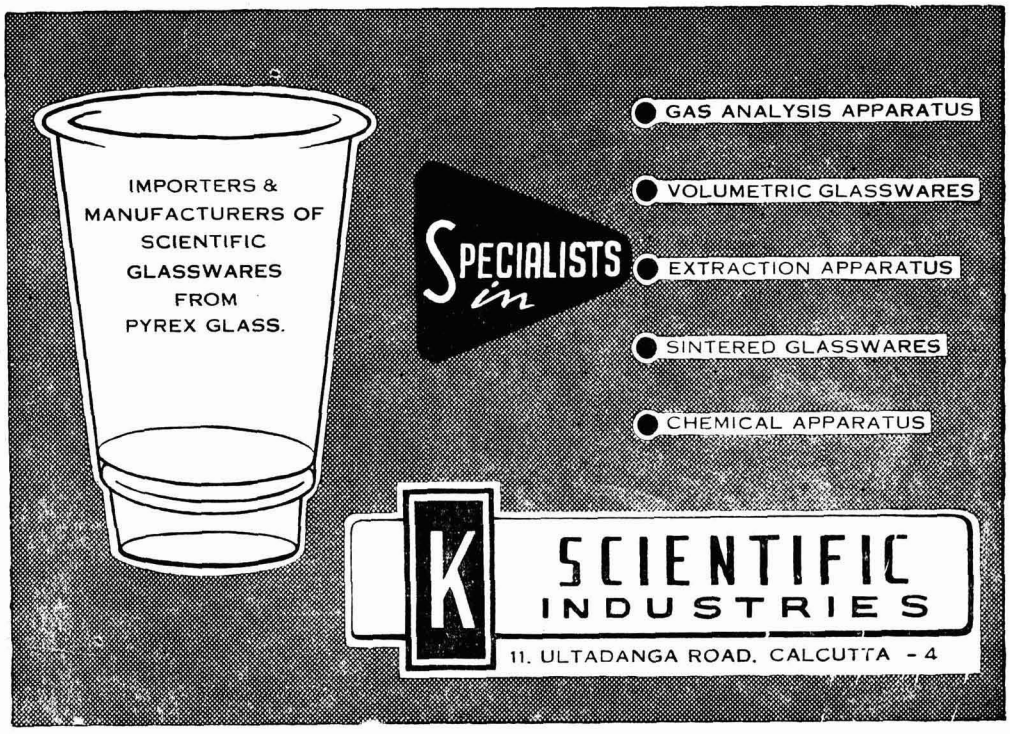

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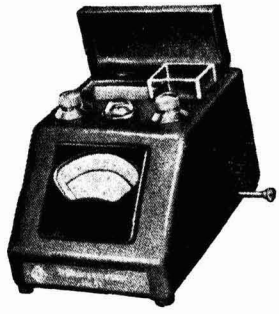

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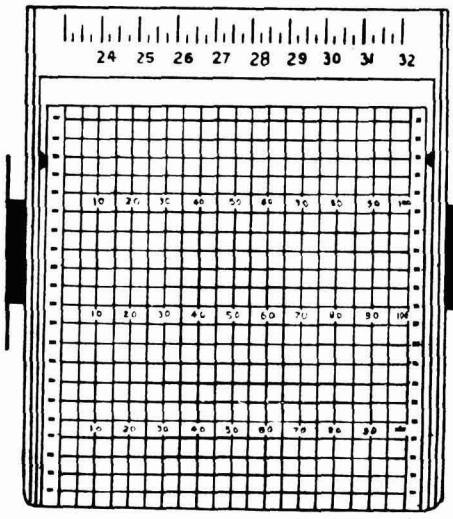

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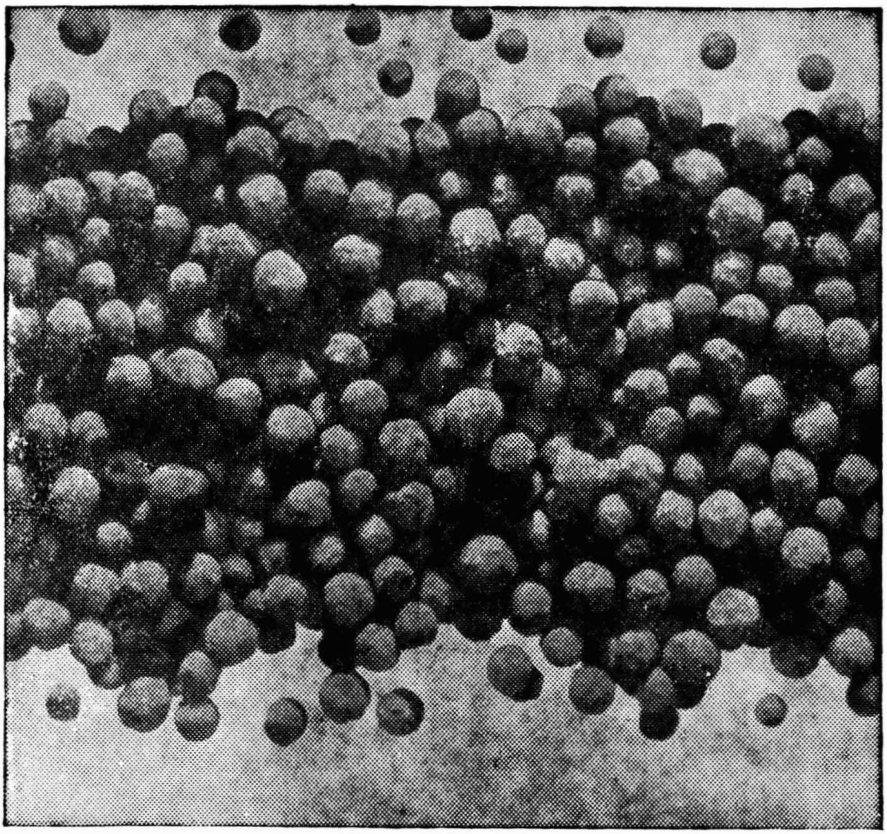

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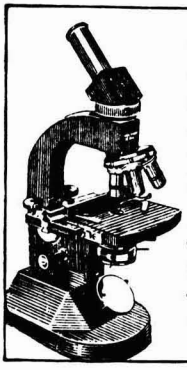

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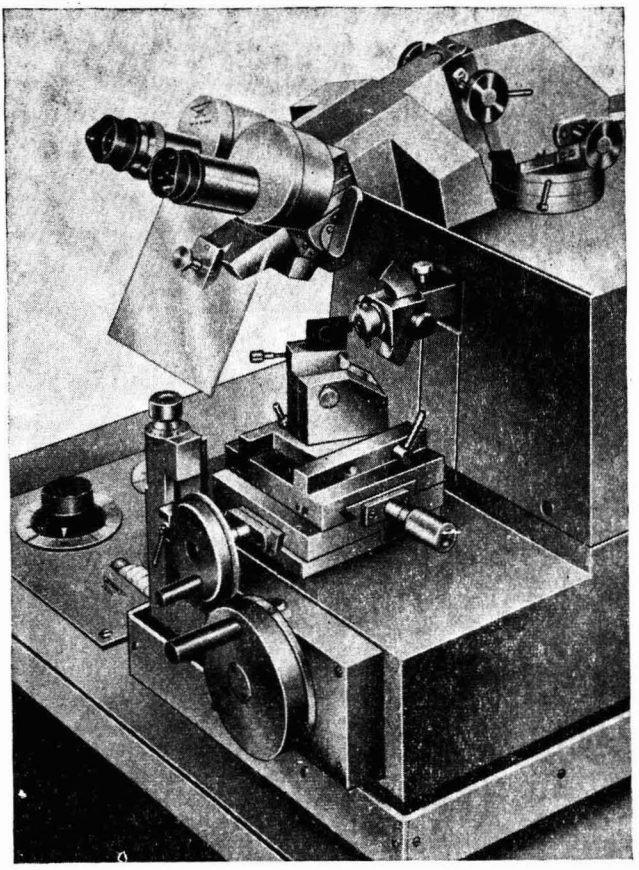

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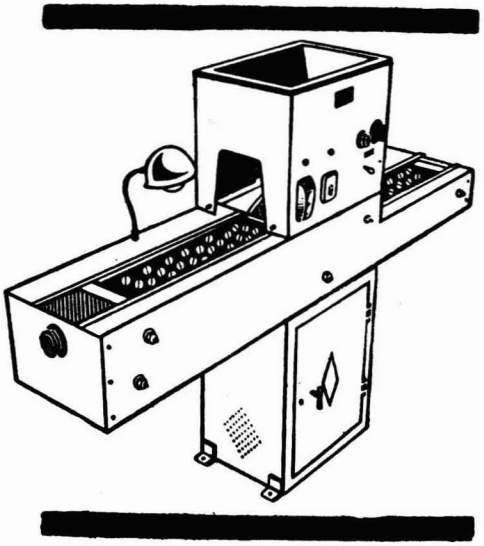

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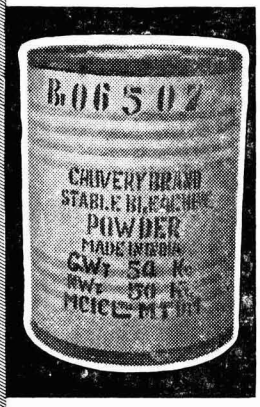

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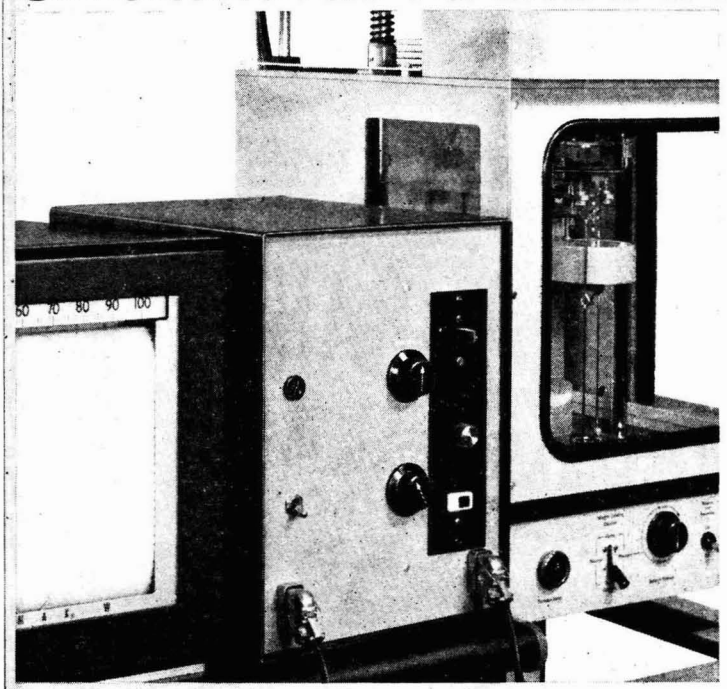

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