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JOURNAL OF THE MALTA MEDICAL STUDENTS' ASSOCIATION

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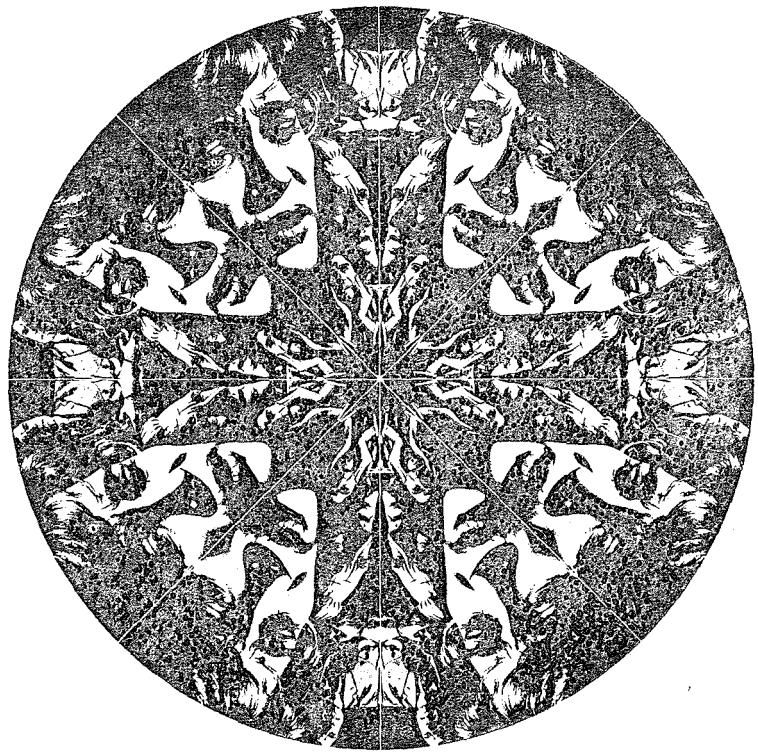

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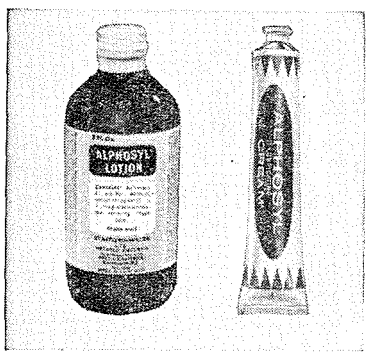

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References: 1 Clin Med. 5-485, April 1958–Alphosyl Lotion. 2 Ann. N.Y. Academy of Sciences, 73:1028, Nov. 1958. 3 Report to Conf on Psoriasis, N.Y. Acad.Sc. May 9, 1959. 4 Ohio St. Med. J. 55:805, June 1959–Alphosyl Lotion. 5 Clin. Med 8:9 Sept. 1961–Alphosyl Cream. 6 Skin, March1962 –Alphosyl Cream.

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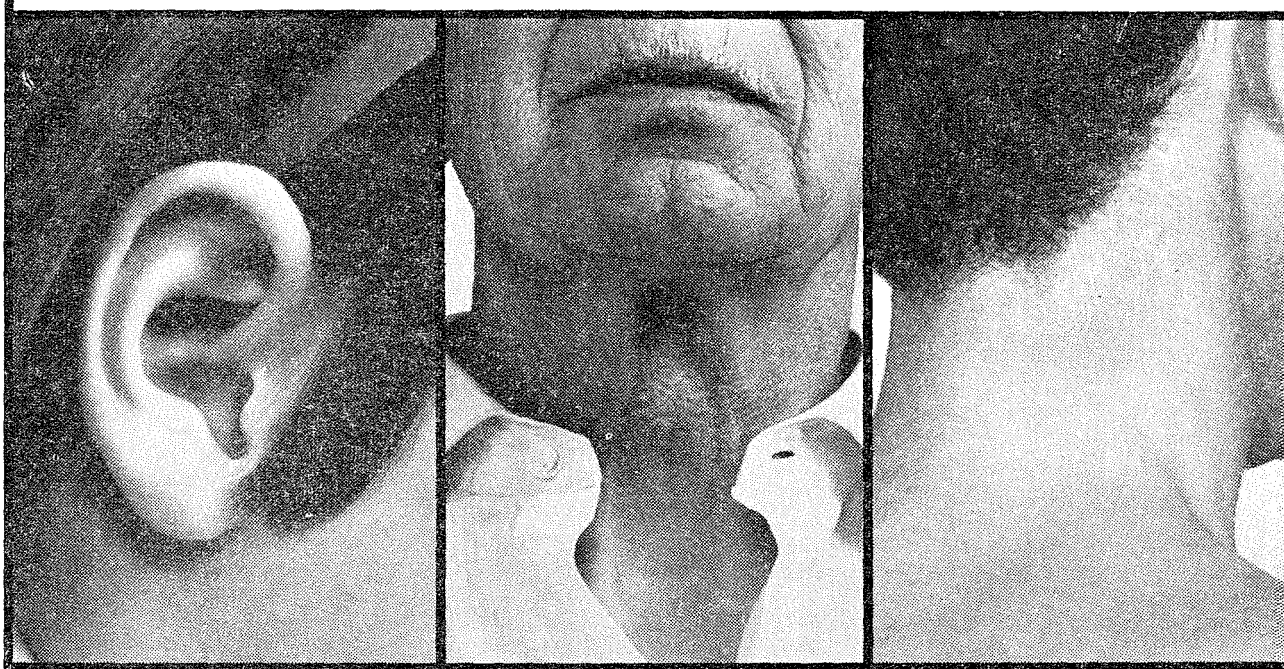

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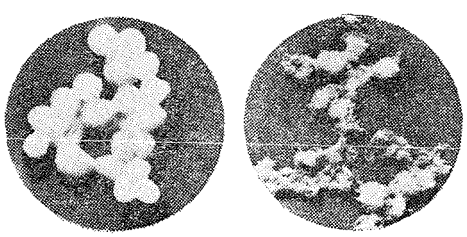

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The Chest-Piece

CONTENTS

Editorial ... page 7.
The Role of Insulin in Diabetes Mellitus
R. Ellul Micallef ... " 9
Medical Summer School in Scandinavia
Peter Cauchi ... " 21
Letter to the Editor ... " 28
Pathology in Glasgow
T. Busuttil ... " 29
An Introductory Excursion into Statistics
V. Cremona M.D. ... " 31
The Use and Abuse of Anticoagulants in Myocardial Infarction
R. Soler ... " 39
The Development of Medical Jurisdiction
M. Narrainen ... " 45

EDITORIAL

My predecessor noted that important changes were taking place in medical teaching in Malta. Changes and development plans are affecting the whole university, however, the Faculty of Medicine is particularly involved. The new biennial courses have resulted for the first time in two courses being at the clinical level together. St. Luke's hospital now has over 80 students in its wards. The facilities of the Medical school are gradually coming into use more and more. The re-opening of the canteen was very welcome. At present it shuts at 2 p.m. An extension of this time is desirable. After an afternoons' work in the wards or laboratories some refreshment should be available before the last lecture of the day.

The topic of lectures was also raised by the previous editor. The term opened in October with a time table of 45 minute lectures. This was an immediate success. It is hoped that it will not be gradually forgotten with time. Another progressive measure which should not be discarded is the provision of time for library study. It is unavoidable that the present Junior-Final course should be the subject of experiment in such a time of development and change. The above measures have proved a success and should be retained. The pumping of new knowledge into the student especially in the first term of the Junior course could be taken at a more gentle rate. Tutorials and demonstrations can do much to arouse the students' interest in his work and should occupy a more prominent part of the time-table at present dominated by lectures.

For the first time, March examination sessions for certain Final course subjects will be carried out this year. The spreading out of the examination load is welcomed by the student and it will be interesting to see whether it is accompanied by an improvement in the mortality rate in March and June.

A last word on clarking abroad. The medical students have a very active exchange staff ready to help them spend the summer months in some hospital abroad. A chance to see how others work and and think can be a valuable part of the course, and should not be missed by anyone who has the opportunity to go. The idea is not to have a cheap holiday, but to learn — and to learn in a pleasant way, gather new experiences and make new friends. This, need not necessarily be limited to the clinical courses only. We play host to a large number of foreign students every year and only send a handful of our own abroad. Now that there are over a hundred medical students, we hope that more will take advantage of the facilities offered.

MOGADON* AND NATURAL SLEEP

Striking advances have recently been made into the knowledge of sleep with the aid of the electroencephalogram, and it is now recognised that sleep does not consist of a quantitative reduction in cortical activity but of a qualitative change. Hypnotics, by their generalised depressant action on all the brain structures, greatly reduce cortical activity and sleep takes on an abnormal pattern. The development of Mogadon, however, has now made the treatment of insomnia possible without any significant lessening of cortical activity. The sleep induced closely resembles natural sleep; there is no disturbance of the normal rhythmical balance that exists between the sleep and wake processes and the patient will awake refreshed, without hangover and without mental confusion.

ROCHE

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The Role of Insulin in the Pattern of Diabetes Mellitus

— *by R. ELLUL MICALLEF* —

— *"Degiorgo Prize for Therapeutics, Pharmacology and Materia Medica"* —

Historical Background

Diabetes mellitus has been known to exist from time immemorial. It was recognised in ancient Egypt and has been found described in Indian Sanskrit Verdic literature as "the passing of urine with honey". Aretaus (1st century A.D.) gave the first classical description of the disease and laid emphasis on the large amounts of urine passed — hence the term diabetes, from the Greek for siphon. It was left to Thomas Willis who, recognizing the importance of sugar in the urine, added the term mellitus — Latin for honeyed — in 1674, thereby distinguishing it from the insipid variety. Chevreul in 1815 finally defined the nature of the reducing substance in urine of diabetics to be glucose.

Later, Cawley Bright, and others pointed out the association between Diabetes mellitus and changes or malfunctioning of the pancreas. This was confirmed in 1889 by the German physiologist Oscar Minkowski; he and Von Mering found that pancreatectomy in dogs caused a condition which strikingly resembled Diabetes mellitus in man. In 1869 Paul Langerhans had previously discovered special specific cells which appear as nests or islets in the pancreas, and in 1916 Sir Edward Shafer suggested that these islets secreted some substance controlling the metabolism of carbohydrates, and coined the name INSULIN for this substance. For many years, attempts to extract and isolate insulin met with nothing but failure and frustration. Eventually, a young orthopaedic surgeon, the late Frederick Banting, working with Charles Bets, then a medical student, in Macleod's laboratory in Toronto, succeeded in 1921 by ligating the pancreatic duct thus producing degeneration of the acinar part. The pancreatic beta cells had at last been made to yield their valuable hoard. Insulin was first used on a human subject on January 11, 1922, the patient being a young diabetic doctor, Joe Gilchrist. These extracts were still unpredictable in terms of toxicity and potency and it was only in 1926 that insulin was first obtained in its crystalline form by Abel and Geiling. In 1955 Frederick Sanger succeeded in elucidating the chemical structure for which he was awarded the Nobel Prize 3 years later. Claus Hocman in Pittsburg in 1963 succeeded in synthsizing insulin in the laboratory for the first time.

Structure, Action and Role of Insulin in the Metabolic Pathways.

The insuling molecule consists of two polypeptide chains — a glycine chain, Fraction A consisting of 21 amino-acids and in internal S-S bridge; and a phenylalanine chain, Fraction B containing 30 amino-acids; the chains being connected by disulphide (S-S) bridges of cystine residues. Up to recently, the rate of insulin releases appeared to be mainly a function of the blood glucose concentration; it falls with hypoglycaemia and rises with hyperglycaemia. It is not known whether the insulin concentration of the blood perfusing the pancreas also serves as a negative feedback mechanism. The beta-cell membrane is apparently freely permeable to glucose but it is uncertain whether the release of insulin is controlled directly by the intracellular concentration of glucose or of one of its metabolites. Lately it has been proved that plasma insulin levels are higher with intestinal-intrajejunal - administration of glucose than with intravenous glucose, despite much lower blood glucose levels. This suggests that factors other than arterial glucose con-

centration may be involved in the regulation of plasma insulin levels. The most likely explanation seems to be the release of a humoral substance from the jejunal wall during glucose absorption which acts, along with a rise in blood glucose, by stimulating the release of insulin from the beta-cells. Insulin is stored in the beta-cells as encapsulated granules (Hartroft & Wrenshall, 1955).

The E/M has shown that liberation of the granules from the cells is a relatively simple process. The earliest change is a margination along the plasma membrane of the cell by the granules encased in their smooth membranous sacs. The smooth sacs encascasing the granules fuse with the cell membrane, and rupture; the granules are liberated into either the intercellular or pericapillary space. The granules apparently undergo rapid dissolution since they are no longer visible by E/M in the extracellular space. This process of simple ejection of the granules into the E.C.F. is called emiocytosis. The synthesis of the beta granules appears to occur within the ergastoplasm of the cell.

The main effect of insulin is of course the reduction in the blood glucose level mainly by encouraging peripheral utilisation of glucose especially by the muscles and by favouring glycogenesis in muscle and adipose tissue. In contrast with the well established action of insulin on muscle and adipose tissue, its effects on glucose metabolism in the liver remain inconclusive and a matter of controversy. A large body of evidence indicates that insulin plays a role in controlling the hepatic output of glucose; the question whether insulin stimulates hepatic glucose uptake remains largely unsettled. The magnitude of the effects and sites of action of insulin on hepatic glucose metabolism are still uncertain. DeBodo has recently determined that insulin inhibits glucose production by the liver. Formerly it was thought that insulin achieved the promotion of glucose utilisation by enhancing the hexokinase reaction (Cori 1946) wherein glucose is converted to glucose-6-phosphate, the only form in which it can be utilised for energy production, or stored as intracellular glycogen. It appears now, that there is no ground for supposing that insulin activates hexokinase or removes a physiological inhibition of this enzyme. Levine and Goldstein in 1960 have postulated that insulin primarily stimulates the transfer of glucose across the cell membrane rather than acting on specific intracellular enzymes. Muscle cells, fibroblasts and adipose tissue do not permit the rapid free entry of sugars; rather the cell membrane possesses a specific transport system which carries glucose into the cell interior at a rate greater than can be explained by simple diffusion. This transport system requires the presence of insulin; insulin in effect can be imagined to open a sort of trapdoor which permits glucose to enter freely. Neurones and erythrocytes can transport glucose across their cell membrane without insulin Cells of the intestine, liver cells and perhaps also those of the renal tubules can transport glucose without insulin. If there is any direct action of insulin on carbohydrate metabolism of the liver cell, it does not seem to be related to cell membrane transport (Levine 1965).

It must be remembered that insulin is not the only agent which facilitates sugar transfer. Clinical experience and the more recent experimental work by Ingle have shown that muscular exercise can also bring about this transfer in the absence of insulin.

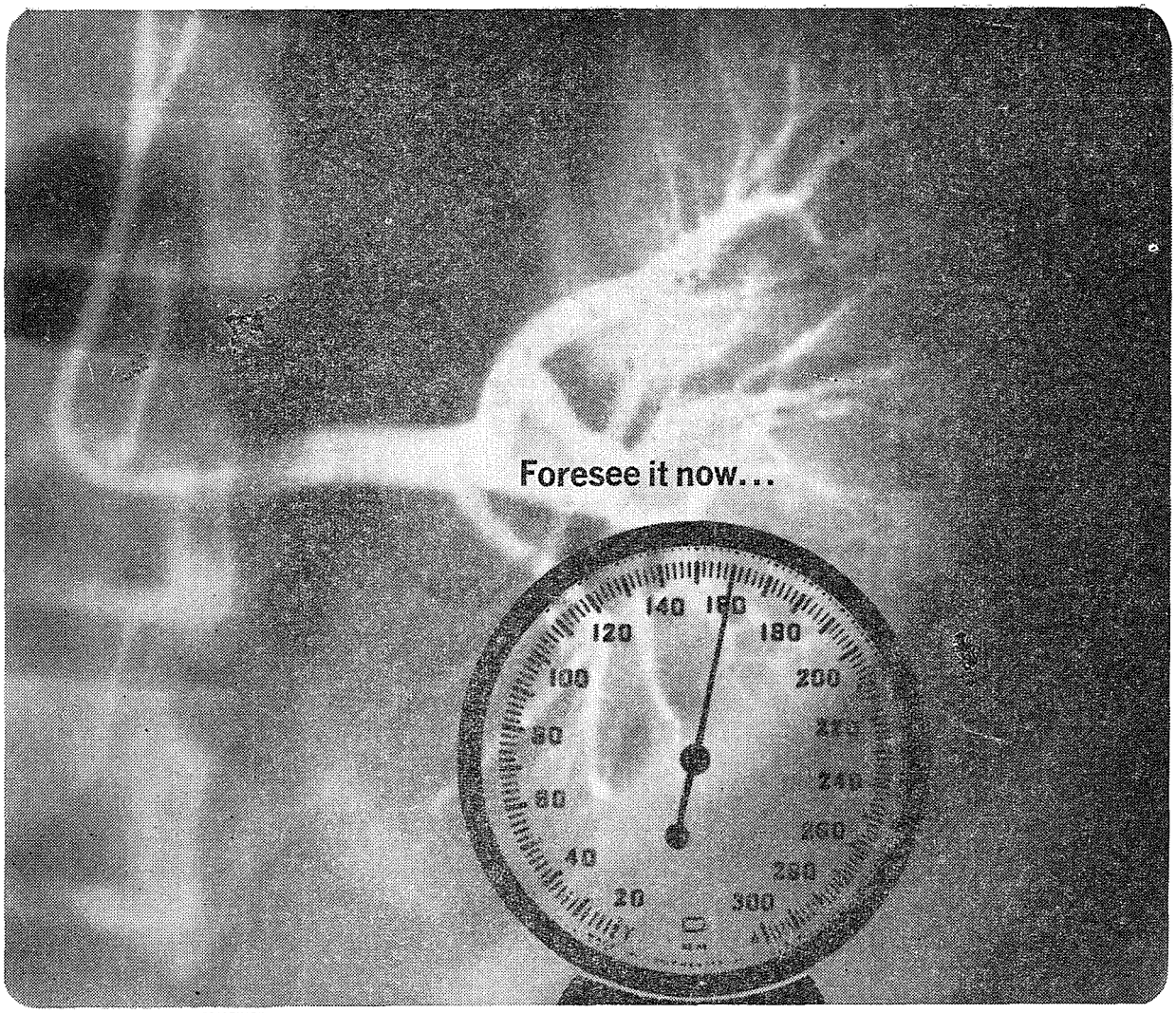
If glucose does not easily enter the cell there is a decrease in the normal intracellular metabolism of glucose which in turn leads to disturbance of liquid and protein metabolism. Chain (1960) has also suggested that insulin exerts a specific stimulating effect on a number of energy-requiring reactions involved in the synthesis of glycogen, fat and protein. Once intracellular glucose has become phosphorylated to glucose-6-phosphate it cannot leave the cell. Glucose-6-phosphate may either be converted to glycogen or be broken down via the classical Embden-Meyerhof pathway to form acetyl-CoA which may either provide energy via

the Krebs cycle or act as substrate for the syntheses of fat and protein. In adipose tissue, and to a lesser extent in the liver, there is an important alternative metabolic pathway for glucose-6-phosphate, the hexose monophosphate shunt. Insulin may also have a direct effect on protein metabolism by stimulating directly protein synthesis. Insulin is inactivated by degradation, this is in contrast to the inactivation of the steroid hormones in which the conjugation mechanism plays an important part. The degradation of insulin appears to be due to a preliminary reductive cleavage of the S-S bond by a glutathione-insulin-transhydrogenase and a subsequent hydrolysis of the resultant A & B chains. Hypophysectomy decreases this degradation and this may in part account for the insulin sensitivity in panhypopituitarism.

The Use of Insulin in the various patterns of Diabetes mellitus.

Diabetes mellitus is a syndrome with a variety of causes, all having in common hyperglycaemia from an impaired glucose catabolism, with consequent glycosuria, polyuria and dehydration. Secondary alterations in fat and protein metabolism lead to tissue wasting, ketosis and coma in the uncompensated state. The central metabolic lesion lies in the underutilisation of glucose as a consequence of an absolute or, more often, relative lack of insulin. Following Banting and Best's brilliant contribution, it soon began to be realised that insulin is not the whole solution to the problem of Diabetes mellitus. Diabetes research has shared in the general ferment of biochemical investigations during the past one or two decades, yet its aetiology remains as much as an enigma today as forty years ago; indeed even more complexities are nowadays evident. Diabetes mellitus not only manifests itself in the form of metabolic abnormalities but is also expresed as a strong susceptibility to arteriosclerosis and to certain rather distinctive lesions in the kidneys, retinas and elsewhere which are characterized chiefly by microangiopathy. There is a definite genetic disposition to the disorder but a syndrome with similarities at least in the metabolic aspects makes its appearance following pancreatectomy or chronic pancreatitis and in conditions associated with excessive secretion of certain hormones notably growth hormone and the glucocorticoids. The exact mechanism responsible for insulin insufficiency in Diabetes mellitus is unknown. It has become increasingly evident that a primary defect in beta-cell function cannot be responsible for the insulin insufficiency in the majority of patients. Theoretical possibilities include blockage in the formation of insulin or in its release from the pancreas, blockage of its passage through any one of the various membranes, neutralization in the bloodstream, excessive degradation, excessive amounts of opposing hormones and inability of the tissues to accept or to utilize it. The diminished reserves of insulin in the islets of many diabetic patients appears to develop secondarily to a chronic drain induced by extrapancreatic factors such as inactivators, inhibitors and perhaps antagonists of insulin. The possibility that Diabetes mellitus may be due to the inheritance of abnormal plasma proteins — insulin antagonists has been raised by Bornstein and J. Vallance — Owen (1964). However, there is still lack of definitive evidence and it is becoming increasingly difficult to envisage Diabetes mellitus as a disease due to such a single factor. F.G. Young has brought out evidence supporting the view that an abnormally high level of serum Growth hormone may be an important factor in some cases of diabetes. This has been confirmed by Randle.

Diabetes mellitus exists chiefly as two main clinical varieties: Type I is the diabetes of acute onset in young usually thin people rapidly leading to severe ketonaemia, coma and death unless treated with insulin. This is known as the juvenile type of diabetes. Assay of the insulin activity of the plasma, using the rat diaphragm or the rat epididymal fat pad, shows none to be present, this was first carried out by



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It's never too soon to consider renal damage because the great majority of hypertensives have some renal vascular impairment, even those with only mild sustained hypertension. "Although renal blood flow is presumably normal at the onset of essential hypertension, progressive impairment in renal blood flow and glomerular filtration rate is an inevitable consequence of sustained diastolic blood pressure elevation."[1] ALDOMET provides smooth effective antihypertensive control around the clock *and* "... produces a consistent decrease in renal vascular resistance which maintains renal blood flow when the arterial pressure is reduced."[2]

1. Brest, A. N.: Hemodynamic response to antihypertensive drug therapy, J.A.M.A.: **192**: 127-130, April 15, 1965. (U.S.A.) 2. Onesti, G. et al.: Comparative hemodynamic effects of antihypertensive agents: alpha-methyldopa, pargyline and isocaramidine. Abstracts of the 37th Scientific Session and 18th Annual Meeting, Council on Arteriosclerosis, American Heart Association, October **33**:III-135, 1964. (U.S.A.) **Note:** Detailed information is available to physicians on request.

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Bornstein & Lawrence, then by Vallence Owen. Type II is the diabetes of gradual onset, in older, usually obese people and occurring more frequently in women. This is due to a relative rather than an absolute insulin lack. Plasma assay shows near normal insulin activity. This is the maturity onset type of Diabetes mellitus.

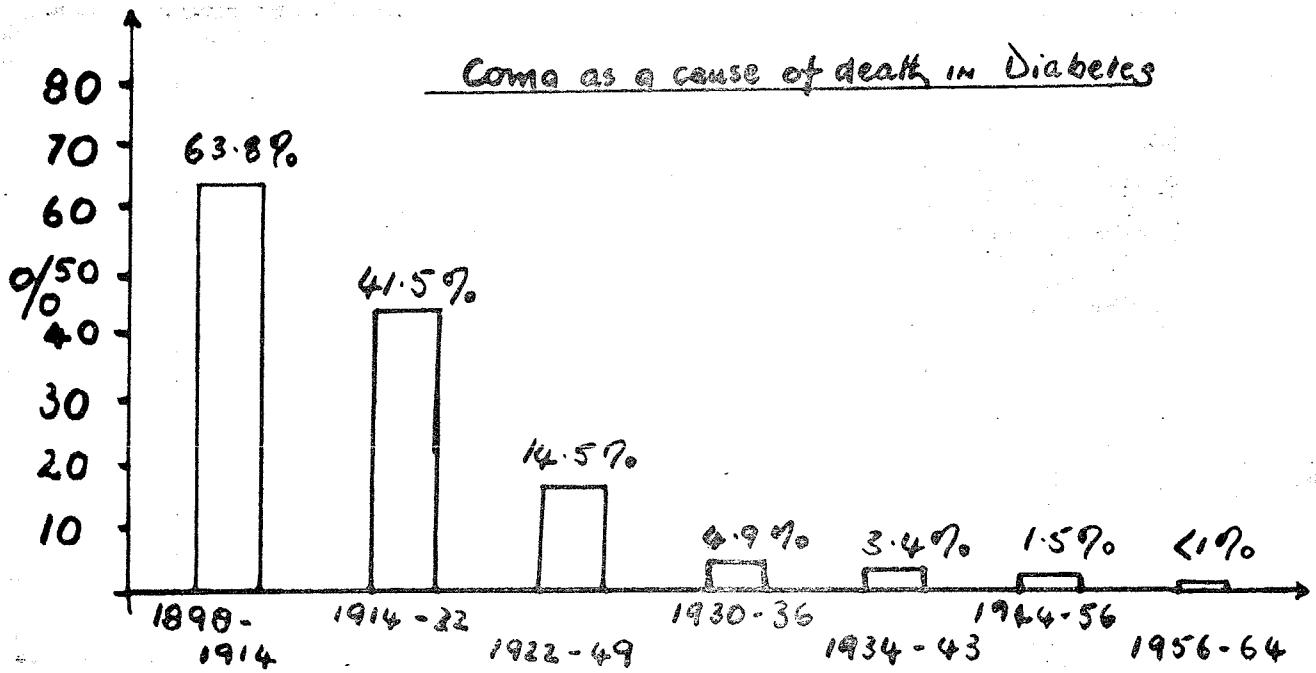
Juvenile diabetics require treatment by both insulin and diet, and need to have these matched to the amount of physical exercise they take daily. Clearly a heavy manual worker will need more insulin and more calories than a clerk. For adequate control a regular amount of activity and a regular diet are essential, and certain occupations, such as commercial travelling, are best avoided. Each case must be judged on its own merits and adequate treatment administered per individual: as the juvenile type of diabetes is particularly unstable. Besides physical activity of the diabetic, when considering the number of calories needed, such factors as age, sex, weight and height must also be taken into consideration. Carbohydrates must not be restricted too rigorously, as too little promotes gluconeogenesis, imparts glucose tolerance and decreases insulin sensitivity. Dunlop recommends 100 grams of carbohydrates for every 1000 calories of the diet. Perhaps nowhere better than in Dr. Lawrence's article "I have lived for 40 years the life of a diabetic patient" can one understand and appreciate the the great role which insulin has come to play in the day to day life of a juvenile diabetic. Before 1921, the juvenile diabetic used to eke out a miserable existence for a few years on semi-starvation dietary regime. Dr. Lawrence who was up till recently Director of the Diabetic Clinic in King's College Hospital, London, describes how he had to give up a promising surgical career and go to Florence, where he was always on the brink of passing into coma and unable to do any solid work. The discovery of insulin changed completely the whole aspect of his life and enabled him to further his medical career as well as to participate most fully in the world around him.

The maturity onset type of diabetes is usually well controlled with diet, with or without the administration of oral hypoglycaemics; sulphonylureas or the diguanides. Both phenformin and metformin — the diguanides — and carbutamide, tolbutamide and chlorpropamide — the sulphonylureas, are not without toxic side effects. Diabetics treated on such a regime are those having a stable type of diabetes who are not prone to develop ketosis. Patients with adult-onset diabetes who cannot be controlled satisfactorily by diet alone or with an oral hypoglycaemic agent, also require insulin. Patients with stable diabetes controlled by diet or an oral hypoglycaemic agent may become uncontrolled and sometimes ketoacidotic if they develop an acute or chronic infection, suffer physical injury, undergo an operation under anaesthesia or become emotionally upset. Under such circumstances they may require insulin temporarily.

A number of insulin preparations is now available differing in time of onset, peak of activity and duration of effect. The first to be produced was Soluble Insulin which has a powerful, rapid but relatively fleeting hypoglycaemic effect, in fact it starts to work in ½ hour, reaches its peak in 2-3 hours and the effect is over in 6-8 hours. It imitates roughly the increased secretion of insulin by the normal pancreas after meals. Longer acting insulins were later introduced by combining insulin with protein and buffer; such preparations include isophane insulin (N.P.H.) globin insulin, Protamine Zinc insulin; the latter was introduced by Hagedorn in 1936. Their effect on the blood sugar is delayed, relatively smooth and prolonged. P.Z.I. taken 4-6 hours to start acting, reaches its maximum in 15-18 hours and the effect is over in 24-32 hours. Globin insulin and N.P.N. are intermediate in action between Soluble insulin and P.Z.I., their effect starts within 2-4 hours and is over in about 24 hours. In 1952 the insulin zinc suspensions (I.Z.S.) were introduced in Copenhagen by Hallas-Moller. It is prepared in either the quick-acting amorphous form; semilente, having much

the same time of action as the globin variety, or the slow acting crystalline form; ultralente, very similar in effect to P.Z.I., but acts a little more rapidly and probably for a shorter time. A third variety is I.Z.S. lente, a cloudy preparation containing 3 parts of I.Z.S. semilente to 7 parts of I.Z.S. ultralente; it starts to act within 1 hour and lasts for about 24 hours. The main advantage of I.Z.S. is that it contains no foreign protein and so is less likely to cause local or general sensitization phenomena. Dunlop recommends that patients who do not require more than 40 units of Plain insulin daily can be well controlled with one subcutaneous injection of I.Z.S. lente before breakfast a day. The vast majority of diabetics requiring insulin are, according to Dunlop, best controlled by P.Z.I. and soluble insulin given before breakfast, about $\frac{1}{3}$ of them will require an additional injection of Soluble insulin before the evening meal. Recently, two new preparations have been put on the market. Actrapid novo insulin, which acts within 15-30 mins. and lasts for about 6 hours; and Rapitard which contains no foreign retarding agents, starts within 15-30 mins. and lasts for about 18 hours. The doses required, vary from patient to patient, and each requires individual management. The education of the diabetic is essential to success in treatment, if possible he must be taught to correlate diet, exercise and insulin doses with various conditions of life.

Diabetic coma is always a medical emergency, the patient should be hospitalized without delay and as soon as he arrives the patient should receive 50 units of soluble insulin intravenously and a further 50 units subcutaneously. Supportive therapy is of course instituted at the same time, this includes amongst other things intravenous infusion with isotonic saline, antibiotics and replacement of Potassium if necessary. After blood glucose estimations, the patient is to be treated accordingly with further doses of soluble insulin until stabilized. Further appropriate treatment with other insulin preparations is of course later instituted. Diabetic coma as a cause of death in diabetics, has nowadays fallen down rapidly from about 64% in the early 1900's to below 1%; the advent of insulin, together with increased advance in the field of biochemistry has profoundly altered its incidence.



Up to 50 years ago, most diabetic women were infertile; with the advent of insulin this too has changed to some extent and an increasing number are becoming pregnant. Insulin has rendered pregnancy relatively safe for the diabetic mother, in fact in pre-insulin days mortality was about 45%, now it is less than 1.5%; but the child is often born macerated and dead or dies soon after.

Insulin requirements usually increase sharply for the first trimester, remain steady for the second and usually increase for the third. It is particularly important to remember that the insulin requirements fall dramatically after delivery, so that the dose should be drastically curtailed as otherwise hypoglycaemia sets in. Infections also result in increased insulin requirements. Diabetes in children is exceptionally difficult to treat and keep under adequate control. Perhaps the most suitable regimen, according to Dunlop, is the daily injection of P.Z.I. and soluble insulin before breakfast and the administration of a second dose of soluble insulin before the evening meal. The dose of the morning soluble insulin is based on the pre-lunch and pre-supper urine tests, that of the evening on the pre-bed test and the dose of the P.Z.I. on the true-fasting urine test.

The Changing Pattern of Diabetes Mellitus

The pattern of the causes of death among diabetics has altered radically since the introduction of insulin in the early 1920's and that of anti-biotics in the early 1940's. The two major hazards of diabetes, ketosis and intercurrent infection can now be effectively controlled. Tuberculosis, which undoubtedly was responsible for the death of about half the patients 50 years or even a generation ago in many large city hospitals of the North, has now dropped to 0.2%. Diabetic coma has fallen from 64% to below 1%.

The prevention and treatment of the vascular complications is now the chief problem. Vascular disease in the heart, brain and kidneys is now responsible for at least 75% of the deaths in diabetics. In America the vascular component of diabetes occupies the sixth or seventh place as the cause of death and its ocular manifestations take more people to ophthalmologists than does any other disease and is the third leading cause of blindness in the U.S.A. The basic lesion in these vascular complications consists of a proliferation of the intimal endothelium and a thickening of the basement membrane which histochemical techniques have revealed to contain a high polysaccharide content. Possibly microangiopathy is due to a seepage of polysaccharides from the circulation through foci of capillary damage. This diffuse capillary disease may effect the kidneys resulting in nephropathy, one form of which is the Kimmelstiel-Wilson lesion, first described in 1963 and characterized by cosinophilic nodules in the glomerular tuft; the eyes-retinopathy, the most characteristic abnormality being the microaneurysm, first described by Mackenzie & Nettleship in 1877; and the nervous system — neuropathy. A long standing question still remains without a satisfactory answer. Are the vascular lesions a consequence of the metabolic derangement or are these independent defects? Mirsky, Ellenberg, Spiro and others are now of the opinion that the renal lesions in diabetes mellitus, as well as extra-renal micro-angiopathy are genetically determined features which are independent of rather than a a consequence of, the defect in carbohydrate metabolism. The hyaline changes in or beneath the basement membrane of the islet capillaries are regarded as an expression of the generalised microangiopathy and are responsible for the ultimate abnormalities in insulin secretion. S. Berson in the Banting Memorial lecture of the American Diabetic Association for 1964 states that the relationship between adequacy of control of the blood sugar level and the development of such pathological lesions remains difficult to evaluate because of the arbitrariness and subjectivity involved in deciding whether "good control" has existed. Although the control of Diabetes mellitus cannot be related

definitely to the development of vascular damage, a rapid and severe course of events may develop following a period of poor management. Clinical evidence seems to point out that inadequately treated patients are apt to develop these vascular complications earlier and to a severer degree. The hypophysis is also coming more and more into the picture since the case described by Poulsen in 1953, where a woman with severe diabetic retinopathy improved dramatically after post-parum hypopituitarism. Both Prof. Russell Fraser of the London Postgraduate Medical School and Prof. Luft of Stockholm, among others, have reported success in carefully selected cases of diabetic retinopathy by pitultary ablation; visual deterioration is usually halted and there is often a lessening of the active features. The incidence of peripheral vascular disease — atherosclerosis—is also higher and comes on at an earlier age in diabetics. The control of Diabetics. The control of Diabetes mellitus in patients with atheroscleresis is quite important especially in the presence of infection or of ulcerative or gangrenous lesions.

From the surveys carried out, it is calculated that there are about 50 million diabetics throughout the world. The first major published survey was carried out in the U.S.A.; at Oxford, Mass., by Wilberson & Krall (1947). Further surveys carried out include the Birmingham survey by ten G.P.'s in 1962; the Bedford survey in 1963 by Prof. Butterfield and lately one in Malta by Prof. J.V. Zammit Maempel. Wilkerson and Krall found a total incidence of 1.4%; Prof. Butterfield an incidence of 12% and Prof. Zammit Maempel in the pilot survey in Malta found the incidence of glycosuria to be 8.9% and the total incidence 19.9%. Insulin in no way affects the incidence of new cases, and as it staves off mortality, it increases the total population of diabetics. As there appears to be a hereditary factor in the development Diabetes mellitus, the numbers vulnerable from generation to generation increase. As death rates from general mortality fall and the number of elderly people rises, the incidence of Diabetes mellitus will also rise since it becomes more common with age. Prof. Butterfield in his report on the Bedford Survey writes that the medical services must be prepared to cater for the appearance of very large numbers of diabetics in the immediate future.

The pattern of the mortality has altered greatly since the advent of insulin. Mortality in the younger age groups has been substantially reduced since insulin began to be more available and be more widely used. For ages up to 35 years death rates are between 1/10 — 1/5 of the levels of the early 1920's The change in mortality from diabetes although due in major part to the introduction and increased availability of insulin, must also be attributed to the availability of anti-biotics and to the more rational approach of dietary treatment. The period of most rapid decline in mortality is the decade 1940-1950; this coincides with the introduction of the sulphonamides (1936 onwards), then of penicillin (mid. 1940's) and eventually of the broad spectrum anti-biotics. These provided effective therapy against infection to which the diabetic is so vulnerable and which upsets so readily his metabolic balance.

Over the past 40 years, Diabetes mellitus has changed from a progressive or even rapidly fatal disease into a controlled chronic disorder with mortality mainly confined to old age. This new picture dates from the isolation of insulin and its further development and refinement during the last decades. We have now moved into a phase of detection drives, with the concept of "prediabetes" assuming greater and greater importance. It is being more and more realized that diabetes is not simply a question of insulin deficiency but of some error in the whole metabolic superstructure of the human organism which still defies definition and elucidation. Althought great progress has been achieved, there are still vast territories to be explored and chartered, especially with regard to the problem of microangiopathies and the further elucidation of insulin antagonists and

antibodies.

I think it is fitting that I should end my essay with the words of one to whom so much is owed by so many, and who has dedicated a lifetime to stimulate work in the field of Diabetes mellitus and the role which insulin plays in the pattern of diabetes, Charles H. Best. In one of his articles, "The future of Diabetes" (1962), he says: "The only acceptable goal is complete knowledge of the situation. Detection drives are very productive and eminently worthwhile, but a comprehensive survey with provision for following all border-line cases for prolonged periods is needed. I state my conviction again that thus far we have not learned how to compensate completely for the loss of physiologic liberation of insulin by periodic injections of it." Although a great deal has been achieved, if the detection of Diabetes mellitus could be carried out in a more widespread fashion, at the earliest possible stage and in a simple manner and if adequate insulin compensation could be provided, the role of insulin might be even more fundamental and the pattern of Diabetes mellitus more profoundly and radically altered.

THE ROLE OF INSULIN IN THE PATTERN OF DIABETES MELLITUS

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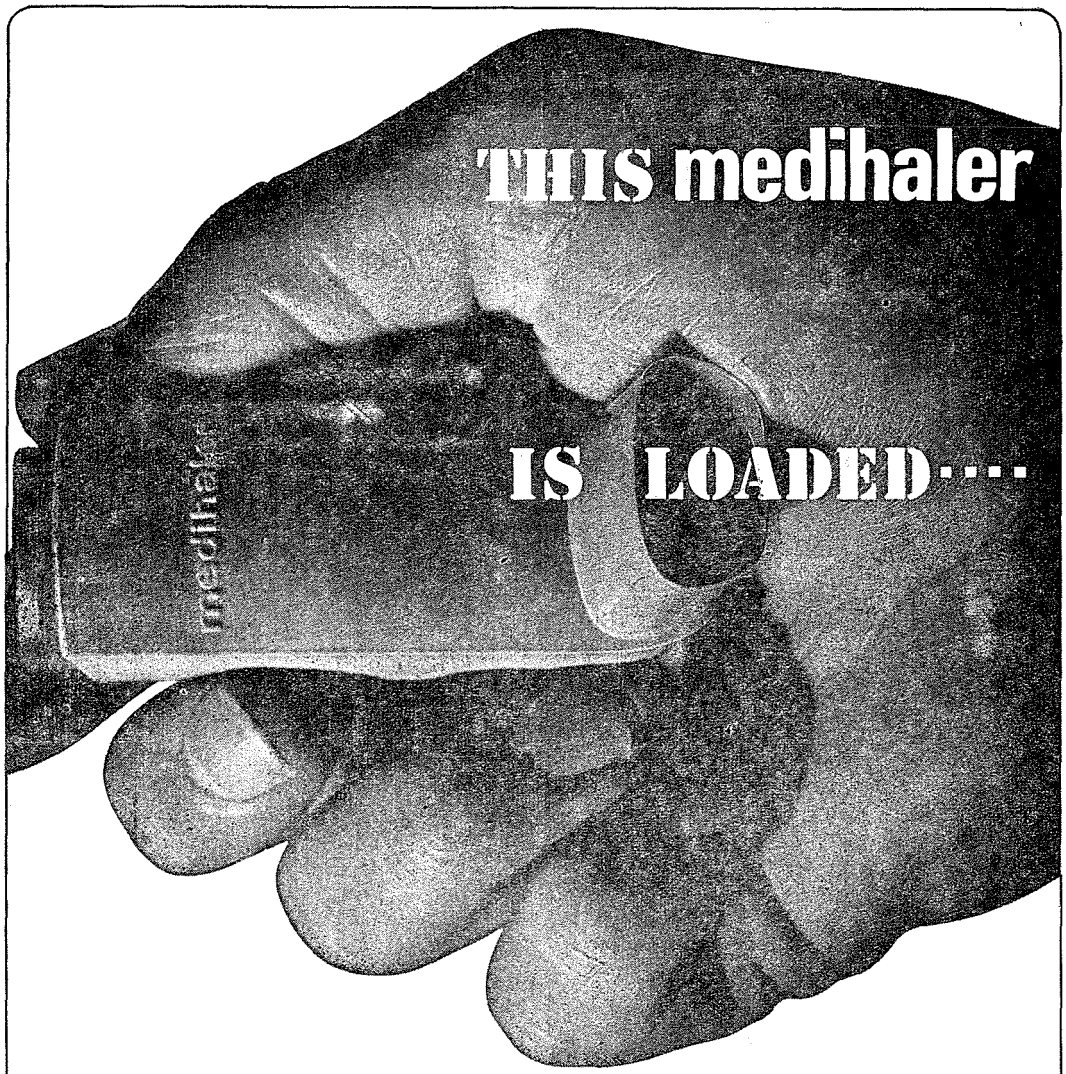

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MEDICAL SUMMER SCHOOL IN SCANDINAVIA

AUGUST 1st TO AUGUST 20th 1966

by Peter Cauchi

The MSSS 1966 was the eleventh one held. The first MSSS was held in 1955 after an agreement reached in a meeting of the member-organisations of the IFMSA of Oslo, Gothenburg, Copenhagen and Aarhus. The Summer School is held every year and the student executive changes from time to time. The features of the course have always been aimed in two main directions: first to introduce foreign students to medicine in Scandinavia and to show them how medical study is tackled there; secondly, and equally important, to provide those taking part with an opportunity to meet each other and to exchange views, in this way providing an increased understanding between young people of different nationalities.

Ten different countries were represented in the MSSS 1966: Scotland, Northern Ireland, Canada, England, Nigeria, Italy, USA, Austria, Western Germany and Malta. The benefits which can be derived from meeting people from so many different countries, and also from different regions of the same country, are innumerable. All the merits and faults of each particular student organisation are discussed; the facilities which some students enjoy over others are compared; the obstacles, financial or otherwise, are learnt. The opportunities of students in different countries to go abroad are compared. The different teaching systems are compared; lecturing, practice, and examinations are held in many different ways and under many different circumstances, each particular system having its big advantages and disadvantages. Of course, many of the advantages and other good things are greatly increased by the economic stability of both the universities and the student organisations concerned.

In order to clarify these points I shall mention some facts I learnt. Some students had part of the fee for the MSSS 1966 paid for. Most of the students abroad, especially those from Europe, do not pay for tuition and are not dependent on their parents for money. All the medical students find jobs in hospitals and in intensive care units; especially in Scandinavia, they are even paid for the clerkships they serve at the hospital. The student in this way also has responsibilities for patients.

Many English teaching hospitals include one month in their stidents' curriculum in which the student can serve a clerkship outside his hospital in any other recognised teaching hospital; students thus have an opportunity of going abroad. Lecturing in Scandinavia does not cover the whole of medicine; it only serves as a lead to students who can then build up their own method of study. Attendance at lectures is voluntary; practical work is mostly compulsory. In Denmark the medical student can extend his course to suit his needs; in fact, he often has to, because he needs to earn money for his living. The course takes $6\frac{1}{2}$ to 8 years. Examinations are taken whenever the student wishes, and when he feels prepared for them. Physics, chemistry, and mathematics are taught on a higher level than with us, in Scandinavia. It is interesting to compare the British system which we in Malta follow most closely, with the American, Central European, and Scandinavian systems of medical instruction. I found it profitable, in particular, to discuss the way medical education is carried out in the United Kingdom; a golden opportunity is provided by the MSSS because of the high number of British students that take part in it.

The various medical topics dealt with include the results of keen research which has been going on for a long time and which is still being done. This result has led to the well known reputation Scandinavian countries hold in the world of medicine, in the fields of radiotherapy and cancer research, in the treatment of shock, social medicine, psychiatry, and neurophysiology. Medical undergraduates in Sweden are far from precluded from the research field, this being reserved to the better ones.

Aarhus.

The topic of study in Aarhus was "Cancer — Research and Treatment". The lectures were mainly given by the radiotherapists, physicists and research workers. We spent all our time at the Radiumstationen of the Aarhus Municipal Hospital, where all the lecturing was done. The first talk was on Orientation concerning Radiumstationen and the organization of radiotherapy in Denmark. The staff of the hospital includes 13 physicians and 5 physicists; they work in collaboration with the general practitioner and specialists from other departments of the hospital on the one hand, and with the specially trained technicians on the other. Thus the patient receives very good care.

In Denmark, the general practitioner can refer a patient to Radiumstationen directly, in this way avoiding a long waiting time in which the tumour flourishes. Various demonstrations of actual treatment, calculation of the correct dosage, and of different apparata and techniques were given. It takes quite a long time, about two to three days, before the patient is ready to get his dose. The patients' condition has to be assessed carefully, and a lot of work is devoted to each individual patient.

We were also shown round the isotope laboratories where isotopes are stored and where such investigations as red cell survival studies, radioiodine uptake by the thyroid, tissue isotope scanning and renography are carried out.

Other lectures given were on Electronic computing in radiotherapy, Lymphography, X-ray treatment of brain tumours, Fibrinolysis and cancer, Environmental factors in Carcinogenesis, X-ray treatment of cancer of the skin, Malignant Lymphogranulomatosis, Chromosome investigations in cancer, and on Testing the safety of a drug with special reference to the use of experimental animals.

A very profitable occasion was an invitation by an Aarhus general practitioner for an evening at his home. there we learnt much about how Medicine is organised in Denmark. This occasion was far from just a medical meeting; we also learnt much about life in Denmark and especially about Danish food, very good examples of which were provided by this family at the delicious dinner they gave us.

The Aarhus students also organised entertainment. An opening dinner got us all together; here we all met each other for the first time, and also met the lecturers. We were also taken to a cruise on the lakes on a pleasure steamer, and in this excursion we were shown Om Kloster, the ruins of a mediaeval abbey; the bones of the monks showed various changes which proved quite a test to our knowledge of pathology. We had an international get together at the Students' House, and one free evening.

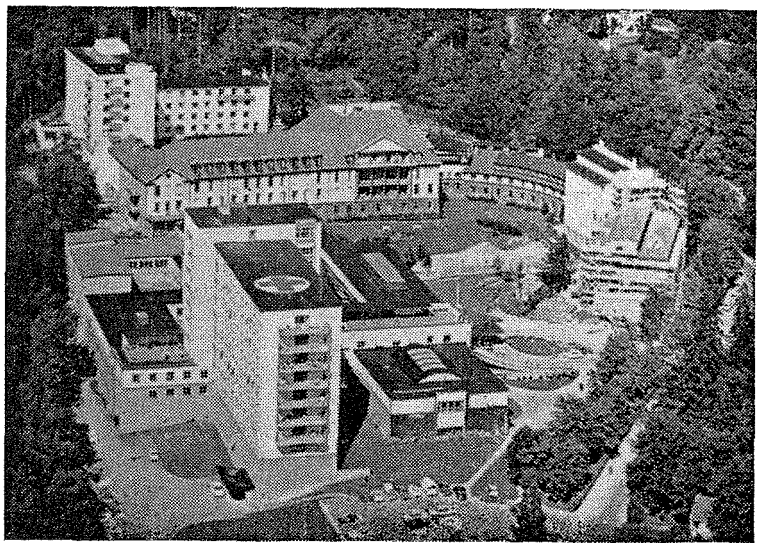
All in all, the organisation at Aarhus was good. What was delightful was the friendly basis on which the medical teaching was placed. In between lectures we had tea-breaks, in which we chatted with each other and with the lecturers, and when we could, take up discussions on almost anything.

Oslo.

Oslo was by far the best stage of the school, both on the teaching side and on the entertainment and social side; board and lodging were also excellent. A word of praise for the wonderful way the Norwegian students organised everything is a must. My impression is that the financial situation of the students in Oslo aided very much to

bring about such a successful outcome. Our lodging was at the Studentbyen, the Students' Town, which consists of flats for students and is used as a hotel for tourists during the summer. The place is very modern, with all facilities, and to my mind it is really impressive. The students' Union was being built, and is very large with modern furniture and games rooms. Students in Oslo do lead a royal life. The food was characteristic including plenty of fish, and very good and plentiful.

The first teaching session was held at Det Norske Radiumhospital, on the more specialised hospitals, located at strategic points. The largest of these is Det Norske Radium hospital in Oslo; attached to the hospital is the Norwegian Hydro's Institute for Cancer Research. All cases of cancer are notified and the particulars are sent to a Central Cancer Registry, so that every case can be followed from the time of its discovery through the various stages of treatment until the patient is cured or dies. All current cases are on record even though the register has been in operation for only a few years. Thus the disease is kept under close observation, and this gives di-



MEDICAL SUMMER SCHOOL IN SCANDINAVIA

treatment of cancer in Norway. As in other places, the treatment of cancer in Norway is based on the earliest possible diagnosis of the disease. Education of the population regarding the latest improvements in diagnosis and treatment and to stress the importance of early diagnosis is carried out on a large basis through two main channels: the public health authorities and the voluntary organisations. A nation-wide scheme for the treatment of cancer is at present under way. Present hospitals are or will become diagnostic centres. Care of certain cases is carried out in three-division or smaller hospitals, but other types are dealt with in larger and rect evidence of the effectiveness of various kinds of treatment, and also allows the authorities to know what is needed in the way of equipment and hospital space for the whole country.

The National Cancer Society is the largest of three voluntary health organisations dealing with problems arising from this disease. It finances a great deal of research and helps with the social problems of cancer patients by providing special social workers who help in the long period of after-treatment or rehabilitation. When discharged from hospital, after a long and exhaustive treatment, the patients are often physically and psy-

chically weak.

We were shown round the hospital, and were demonstrated various radiotherapy equipment and machines. It is built on very modern lines, and provides a very splendid view. The patients live as much as possible like normal people; it is built in a way to provide such an atmosphere. On entering, the hospital looks more like a first class hotel than a hospital. The largest wards are four-bedded; the patients wear their own normal clothes, and pyjamas, and dressing gowns are few.

Dr. Karl Evang, Director-General of Health Services in Norway, gave us an account of the system of public health in that country. There is a National Insurance Institution. All patients pay the minimum possible for their illnesses. Thus about 60 per cent of the fee is paid by the patient for the first two visits at one doctor and the rest is paid by the programme. Hospital care is entirely free; remedial and follow up treatment is also included under the scheme. Medicines are not paid for by the scheme outside the hospital, except for vital and important drugs used in the treatment of specific diseases, such as pernicious anaemia, asthma, and other chronic diseases. Delivery of a new baby will not cost the Norwegian family anything. There are even transportation allowances, and also a funeral allowance, should the best of modern medical knowledge fail. There are cash sickness allowances for sick wage-earners who have to maintain a family.

The opinion of doctors in Norway about the scheme is divided, as is to be expected. In Norway all practicing physicians operate under a system which pays each doctor according to the amount of work he does. Normal rates are set up by the Norwegian Medical Association for consultations, home calls and for different types of examination and operations; these rates are determined after negotiations between the doctors' own national organisation and government authorities. The health insurance programme pays up to three-fourths of these fees, either directly to the doctor, on the basis of his regular reports on the work he has done, or by refunding the patient the amount due to him after he has paid the entire fee himself.

Social medicine is probably most advanced in Norway. Some excellent results have been achieved in certain aspects of the field, and mention must be made of the excellent maternity service. Norway claims one of the lowest perinatal mortalities in the world. Another good example of the high standard of public health has been given above, in the description of the scheme against cancer.

The main part of the lecturing in Oslo was on Shock, and this was undertaken mainly by Professor O.J. Malmo, who is Professor of Pathophysiology. The lectures included subjects like historical considerations and definition of shock, physiology and pathophysiology of the microcirculation, the macrocirculation in normal and low flow states, neuro-endocrine mechanisms in shock, vasopressors and vasodilators, liver and renal function in shock, haemorrhagic and traumatic shock, burn shock, blood transfusion, and metabolic consequences of shock. The various methods of treatment of shock were discussed .At Ulleval Sykehus, 150 patients with shock, who did not respond to conventional treatment, were given small doses of chlorpromazine and a universal vasodilatation was induced. These patients were saved.

The Norwegian students also organised the best entertainment. After visiting Det Norske Radiumhospital, we spent a weekend at Kongsberg; from there we left for a resort up in the mountains called Knutehytta. Here we enjoyed some magnificent Norwegian scenery with mountains, valleys, lakes, trees, and plenty of green, as well as a wonderful bonfire party and dinner in the evening. On our way back, we visited the silver mines of Kongsberg. In Oslo we had a sightseeing tour; other events included a reception by the Mayor in the Town Hall, a dinner by Nyegaard & Co. A/S at the Norwegian Folk Museum and a visit to Munchmuseet. Even with such a tight programme, we found time for shopping and looking around on our own.

Gothenburg.

Here we had one lecture on Rheology of the microcirculation, which has been studied very closely in Gothenburg; in this lecture the importance of lowering the viscosity of the blood in certain conditions with low viscosity dextran (Rheomacrodex) was stressed. The main subject, however, was Orthopaedics, with lectuers by Professor Moberg. He dealt with hand surgery, taking up reconstruction after trauma, treatment of congenital abnormalities, and treatment of hands deformed by rheumatoid arthrithis. Another lecture on Orthopaedics I had to miss, because together with some ten other students I got lost in Europe's second largest hospital, Sahlgrenska.

From the social medicine aspect, we had a visit to the home for juvenile delinquents, situated off Gothenburg. The home for juvenile deliquents, the Swedes of Gothenburg are very pleased about; they told us it is almost one of Gothenburg's tourist attractions. The home, built on modern lines, houses juvenile delinquents in their teens. These young men, coming from gangs all over Gothenburg, usually the victims of broken families are far from being kept under lock and key. Admittedly the worst ones are, but the closed compartment was not as full as I expected it to be. The morning we spent at this home was very interesting indeed. We had an opportunity to ask questions about the background of these young people, about the results when they are released into the community, and about many other points. We saw the way they occupy themselves, by building boats, and carpentry, and other things besides playing games. At Gothenburg we were also shown round the Physiological Institute, where we were shown the section on clinical physiology and that on neurophysiology, where research is carried out using cats mostly.

The entertainment organised by the Swedish students was different from that in the other places, in so far as we were left more to ourselves. A welcoming dinner at Liseberg started us off; after dinner the group spread out in the wonderful amusement park there. Two other dinners and a sightseeing tour around Gothenburg were also organised for us. A wonderful event, for those who did not fall seasick, was a cruise along Gothenburg harbour to Marstrand, an old seaside resort off the west coast of Sweden; that night we had a crayfish party, which was exceptionally lively. In Sweden, we had some free time for ourselves which was a good thing. What I did not like was a certain number of "extras" we had to pay for, such as drinks at dinner which at times came up to fantastic prices, and a very badly conducted town sightseeing tour by the students themselves.

Copenhagen.

The final destination of the School was Copenhagen, where the medical topics were Social Medicine and Psychiatry. The subjects were dealt with in a more practical way, with less lecturing and more to see.

The first visit was to the Day and Night Hospital Montebello for Neurotic Patients. This hospital has two types of patients: some are kept in the hospital day and night for treatment. This stage is kept to the possible minimum. Others, most of the patients, work during the day, and come in for investigation and treatment during the night, or vice-versa. The hospital is very modern and rehabilitation of the patients by means of occupational therapy was of a high standard. Thus a maximum effort to rehabilitate the patient, and finally place him in the normal environment and society is maintained.

Another visit was to the State Mental Hospital in Glostrup, which is situated not far away from the town, so that a close cooperation with the general hospital there, can be kept. Of the same importance, if not greater, is the close proximity to the patient's environment. The hospital houses 300 beds and has an annual turnover of about 3000 patients. It is built in such a way as to avoid isolation of the pa-

tient at all costs, so that it is an open hospital with very few closed walls. At the hospital we were given a talk on the rehabilitation of the psychotic patient, based mainly on a discussion of case histories between us and a social worker, by the head of the work-therapy department Dr. H. Hoffmeyer, who also showed us around his department. This is a very busy place indeed. Patients were employed in a wide variety of work, from carpentery, joinery, designing, and manufacturing tiles, to electrical and even clerical work. Patients are thus kept busy, and this constitutes a form of treatment and rehabilitation. Very interesting is the fact that they are paid a salary for their work, and that they have their own trade union. Thus patients are treated as normal people as far as possible. Dr. Hoffmeyer also told us that the hospital organises yearly guided trips abroad in the summer for groups of patients, which is a very good move towards anti-isolation of the patient.

We also saw the Maternity Aid Centre at Strandboulevarden, which is one of eleven of its kind in Copenhagen. It provides mothers with personal, legal, and social advice and assistance, besides helping with any other problems that come during pregnancy. Besides this, the centre also provides economic and medical aid to a certain extent.

There are also flatlets, housing unmarried mothers and their children; education of both mothers and children is also provided. Information about statistics and recent trends were given in three talks delivered by a social worker, a psychiatrist, and a clinician. The staff consists of 240 members, 72 of whom are social workers, 30 are physicians and psychologists, 21 are consultants and phychiatrists, besides laboratory assistants and office workers. A lecture on "Anticonception" was also given.

We visited Leo Pharmacutuicals where we had a film and toured the factory. Finally, at Laegeforenigen, where the IMCC has its office, we had a lecture by Dr. Paul Backer on general practice in Denmark.

Lodging in Copenhagen was with private families, mostly doctors', whom we met at a reception at the American Embassy on the first day at Copenhagen. There, we were also given many very useful pamphlets and maps. The local students organised a visit to Tuborg Breweries ,where we tasted the different products after being shown around. The result is probably obvious to you. A world competition of beer drinking was held amongst the students; that famous beer drinking country, Austria, won with honours. Needless to say, there was plenty of ataxia around.

In Copenhagen, probably owing to the way we were spread out over the city and its suburbs, we were left very much to ourselves, and to go where we pleased. The Danish students did not organise entertainment, but suggested where to go. Among the activities were an international get-together at the local union of students, a visit to Tivoli, the main tourist attraction, and a visit to Grundtvig Church, where we attended a concert played on one of the largest organs of Scandinavia. An excursion to North Zealand was also held. There we saw all the magnificent castles, including Elsinore, Hamlet's castle. We swam at Hornbach. The day ended with a visit to the amusement park at Dyrehavsbakken where we had dinner. A farewell dinner-dance was held at Laegeforeningen, the house of the International Medical Cooperation committee where we were all given the MSSS 1966 certificate and whence we all left for our respective countries.

Conclusion.

An account of medical teaching particular to each Scandinavian country has been given. What I certainly missed from the MSSS 1966 was the clinical aspect: we did not have any ward rounds or any clinical demonstrations. However the aim of MSS 1966, has been achieved because an introduction to medicine in Scandinavia has been given. My impression about the different organisations of the student bodies are shown in the table.

	Entertainment	Medical teaching	Lodging	Food	Facilities	Work Strain
Aarhus	++	+	++++	++	+	Worst
Oslo	++++	++++	+++	++++	++++	Moderate
Gothenburg	+++	++	+	++	+	Least
Copenhagen	++	+++	++	++	+	Slight

The secretary-general of the MSSS, Miss Lena Ekenvall, who was Swedish, accompanied us throughout the trip, supervising what was going on, while in each town the respective local exchange officers took charge. The Scandinavian students are to be congratulated for being able to tackle such a difficult task.

The cards have been laid on the table. What the Maltese student should do about it is very important. He should weigh the benefit of an MSSS against all the obstacles he faces, such as personal financial problems, no aid in the way of grants from the local Government or the University, an unfavourable examination system, and the absence of charter flights up to Rome. The latter problem could, with luck, be dealt with by creating friendly terms with such organisations as the Danish International Students (DIS) who provide so many inexpensive chartered flights. An extension to Malta of such flights would depend very much on the response of local students which should not be too bad.

Scandinavian countries, who have such Nobel prize winners in Medicine as Finsen, Fibiger, Krogh, and Dam to their credit, wait for you to go and learn for yourselves.

My impressions about the MSSS 1966 and the benefits reaped from it, have been set out briefly. Money spent on a Medical Summer School in Scandinavia, be it yours or your father's, will always be worth while and will certainly not be wasted.

LETTER TO THE EDITOR

THE "CHEST-PIECE" 1966-67

Dear Sir,

Allow me to comment on the attitude taken by the students in the final year with regards to the proposed Christmas tests, as I am sure that many outside our course have failed to grasp what really was behind it all. I hasten to clarify that I am no official spokesman for the course but as none exists I think I have a right as any to expound my views which, after all, I know to be widely held among my colleagues.

FACTS: For those who are ignorant of the basic facts of the case allow me to give a brief resume' of how things evolved. It was a week or so to the Christmas break when the various departments informed us that we were to have practica-viva tests during the coming weeks. The news hit us like a bolt from a clear sky. A few months after the yearly examination-test session and another few months from the March and June examinations, we were hardly expecting this extra set. they were unpopular from the start. No matter what others may hold, students know that tests always disrupt a preset timetable of study to some extent, and they tend to handicap, rather than help us, when set too close to the finals, besides disheartening the unlucky one with a possible adverse effect in the more important hurdles. We all agreed on this and decided to absent ourselves from the tests after informing the heads of the various departments concerned.

DISCUSSION: Since our primary schooling we have been accustomed to regular end-of-term testing and got to accept them as evils nonetheless, but definitely necessary. We had regular testing in our Anatomy days and we never said a word because we understood their value as stimulants and face-hardeners. We had them in Bacteriology and again in Pathology and we accepted them. Why the rebellion now? For the reasons above.

We were told that we were childish and immature, failing to appreciate, and in no position to determine, what was beneficial to us. That really hit us where it hurts. We had no intention of undermining authority and the majority have nothing against tests as such, provided that they come at the right time.

As a course I do not think anyone can say that we evaded work, and most of us did, and still do, what is expected of us. What I ask permission humbly to suggest, is that students be given some say in matter of curriculum and timetables. This is no great original idea — in fact it is practised in many leading medical schools and universities abroad. As it is, here we are treated no better than school-children, and some people expect us actually to behave as such. Immature — really!

Never are students asked to give an opinion as to what they really profit most and least from. They should know something about it because it is they who have to adapt to so many different ways of teaching and they do not have to be told whose is the best. It is false to believe that most students do not care a fig about their work and would do none if given the choice — nevertheless this seems to be the view some people hold about us. What a disappointingly misunderstood lot we are! The truth is that most of us like our work, and what we are asking for is a chance to enjoy doing it so that we may profit more from it.

Yours truly,
A.T.U.

Pathology in Glasgow

Nostalgically as I write, I cannot but help hearing once more in my ears the "sounds most familiar" during my six-weeks' stay in Glasgow: the University clock from its high perch on the Tower solemnly chiming the half-hours, the loud wails of the sirens of the ships berthed on the Clyde banks, and the rain lashing at the window panes from the leaden sky. This "grim and grabby" city was my first glimpse of the world beyond our shores, but it turned out to be a very unexpected, exciting and worthwhile experience.

I worked at the University Department of Pathology of the Western Infirmary. For the better part of most mornings I was attached to the Post-mortem Room. The latter was a sight in itself: it was built in the conventional amphitheatre style but was equipped with 4 busy p.m.-tables, a closed circuit television system for the benefit of the back-benchers, excellent lighting, plenty of shining stainless steel and running water, and an ultra violet light supply to keep dangerous micro-organisms at bay. (Tuberculosis is still quite common) Pathological material was far from lacking, and in the sixty postmortems I was able to take active part in, I succeeded in seeing a good amount of the material described in Pathology text-books.

The close co-operation of all the members of the staff, the conscientiousness and hard-work of everyone concerned and the vast amount of research work going on in all fields and branches of medical and surgical science left me utterly stupefied and spell-bound. Radio-isotopes, scintillating counters, the electron microscope, genetic and immunological studies were the daily bread and sweat of physicians and pathologists. Fancy a houseman in Malta asking for a triple test for the Philadelphia chromosone in every blessed case of chronic myeloid leukaemia!

The Western was really a rendezvous for post-graduate students from the four corners of the earth. I met a number of doctors from the developing countries in West Africa, and students from Persia, Syria, India, Pakistan, America, Greece, Italy and, to top them all, a chap from Honolulu doing E.N.T. I felt duty bound trying to indicate Malta on a map to most of them!!!

For my very educational stay my most heartfelt gratitude goes once more to Prof. Cappell, to Prof. G.P. Xuereb and to the Royal University of Malta who have made this visit possible. My one great regret is that I have not been able to travel before — I really pity my Maltese colleagues who are financially capable of travelling during the summer months yet do not avail themselves of the clerkships offered through IFMSA.

T. BUSUTTIL.

An Introductory Excursion into Statistics

With refernce to a survey on birth weights

— Vanni Cremona M.D. —
Dept. of Obstetrics and Gynaecology.

Statistical analysis is probably the kind of research most suited to a spare time research worker. All that is actually needed for minor surveys is a reliable source of information, a fair amount of patience and more often than not, a calculating machine.

Most of our students graduate with little knowledge of statistical terms and methods and consequently, very little statistical work has been produced in these islands. This is, a great loss, especially when one considers how Malta, being a small island, would be an ideal site to carry out statistical surveys.

The purpose of this article is not to substitute such an introductory course on statistics, but to clarify a few basic terms commonly used in statistical work. Illustration of the various points shall be made by reference to a survey on birth weights which has been recently carried out in the department. The original goal of this survey was, to establish the mean birth weight of single live-born infants in Malta during 1965 and relating this to gestation time, maternal age and parity, social status and maternal blood pressure. As our sample we collected records of all births from St. Luke's Hospital, St. Catherines Hospital, King George V Hospital and the M.M.D.N.A. These institutions delivered 44% of the total births of 1965. Our sample should provide a fairly accurate representation of births in 1965, but one must point out that if it is intended to establish a national mean birth weight, this sample would be extremely restricted.

After collecting the sample, it was found that records of social status were very vaguely kept, and that the majority had no record of maternal blood pressure. As a result of this we decided to discard these two variables. Birth weights were recorded to the nearest oz. as only a very small number were found to have been recorded accurately to a fraction of an oz. Birth weights were converted to gms. to facilitate the work. Gestation time was recorded in weeks from the date of the last menstrual period. This measure of the duration of gestation is notorious for its inaccuracy, but, up to now it is the best guide we have for measuring the length of gestation and therefore all similar surveys have taken the data of the last menstrual period as the base line for measuring the duration of gestation. Data on maternal age and parity was straightforward. From the original sample all stillbirths, twin deliveries and births for which the complete data was not available were discarded. This reduced the sample to 42% of the total live births in Malta in 1965. ,Table 1.) This sample was then subdivided into male births and female births.

Table 1. Comparison of Sample to Total Birth Weights in Malta 1965

	Livebirths		Stillbirths	Unknown Sex
	Males	Females		
Total in Malta 1965	2922	2706	91	
Sample Reviewed	1276	1171	60	10
Final Sample	1232	1126		

The first step of a statistical survey is to construct a histogram in order that one may easily visualise the distribution of a sample. This was done by grouping the birth weights at 200 gm. intervals (Fig. 1.)

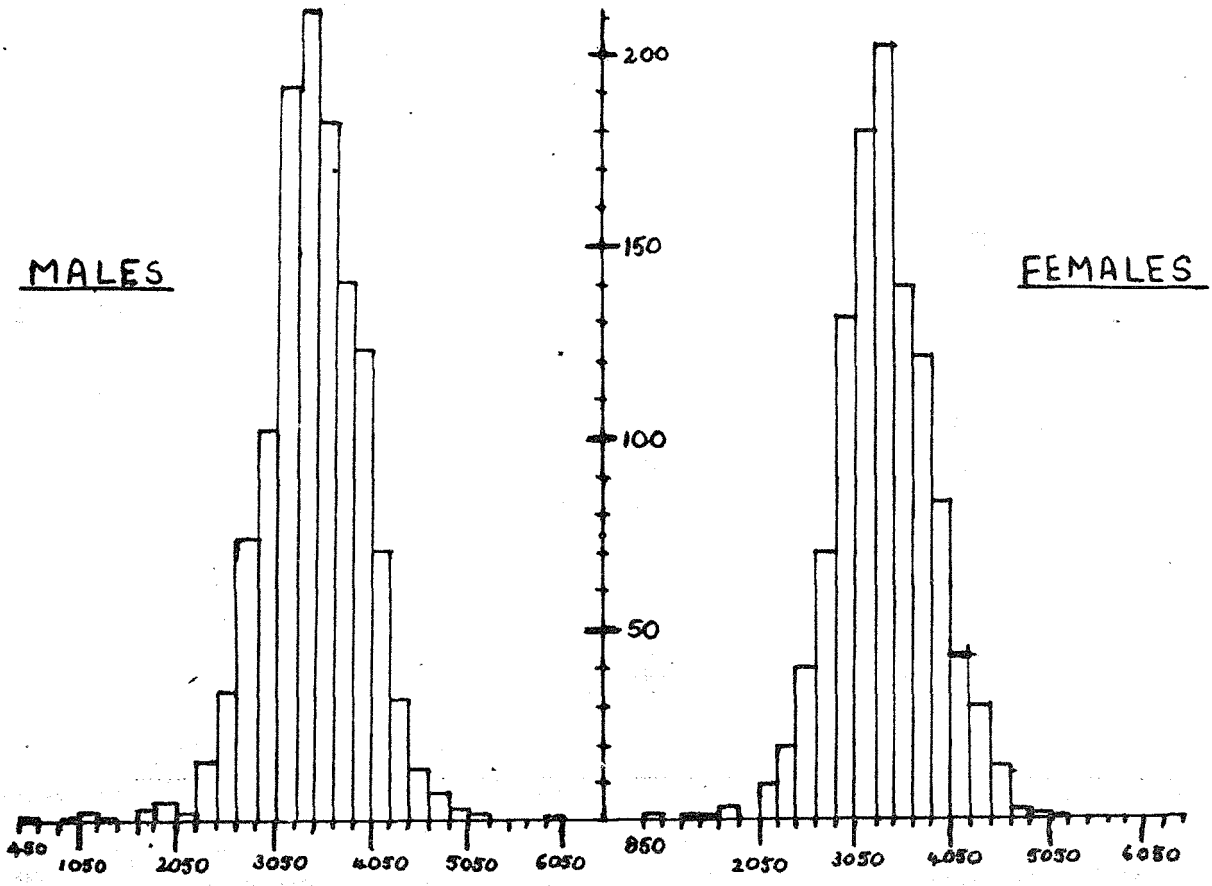


Fig. 1. Distribution of birth weights at 200 gm intervals.

A histogram represents a sample by surface area. The total area enclosed by the columns represents 100% of the sample and the percentage surface area of each column represents the percentage number of units in the particular interval, in relation to the number of units in the sample. In most cases the distribution of a sample will be normal. i.e. there is a regular rise to a peak on one side with a mirror image on the opposite side of the peak. If this pattern were to be transformed into a graph it will show up as a bell shaped curve. However, due to the size of the sample some irregularities are to be expected. Disregarding the peripheral parts of the histograms in fig. 1, it can be seen that there is a slight preponderance of male infants on the right hand side of the peak. However, the female birth weights are represented by a quasi-perfect bell-shaped curve. Small irregularities in the distribution are not very important and these histograms can be said to represent a normal distribution.

If we were dealing with the ideal sample the apex of a bell-shaped

curve would be the mean of the ideal sample. However, as we are not dealing with an ideal sample we have to establish our mean, and then by the use of formulae establish the interval in which we would probably find the ideal mean if we could obtain an ideal sample.

The mean, as everybody knows, is found by adding up all the units in the sample and dividing by the number of units. The mean, however, conveys little information to the reader, as it provides no numerical information of how the sample is distributed around it, i.e. it conveys no information as to whether our sample is widely scattered around the mean or not. This information is represented graphically in the histogram but it can also be expressed as a number and is termed: the standard deviation of the mean.

The standard deviation is defined mathematically as the root-mean-square about the mean, or more simply as the square root of the mean, of the summation of the squared difference of each unit, from the mean of the sample. It would be extremely labourious if we had to find the squared difference from the mean for each unit, but by using special formulae the work is considerably reduced. Apart from the summation of the units, which we already have, all we need is the summation of the squares of the units. By using a calculating machine these two values can be obtained simultaneously. The standard deviation describes the distribution of the sample, because we know that the interval included by one standard deviation on either side of the mean contains about 68% of the sample etc. Thus the mean birth weight for males is 3446 gms and the standard deviation is †-535.4 gms. From this we know that 68% of our sample lies between 2910.6 gms. and 3981.4 gms.

Taking this a step further, we are able to find the standard error of the mean. Should a large number of similar surveys be carried out, the mean values of these samples should be normally distributed with the apex of the curve at the ideal mean. Now by providing the standard error of the mean the exact location of the ideal mean shall not be established, but, provided there are no gross anomalies in the sample, the 95% limits for the ideal mean are established. In other words odds are 19 — 1 that the ideal mean lies somewhere within the interval of the standard error. The standard error for male birth weights is †-15.25 gms i.e. the true mean birth weight probably lies between 1430.75 gms. and 3461.25 gms. The usual way that these values are reproduced is:

Mean †- standard error of the mean (†- standard deviation).

Table 2 Mean Values for Birth Weight, Maternal Age, Parity and Gestation Time

	Birth Weight (gms.)			Mat. Age (yrs.)		Parity		Gestation Time (wks)	
	No.	**Mean**	†-535.4	27.88†-0.18	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**
M	1232	3446†-15.25	†-512.9	28.18†-0.19	†-6.29	2.12†-0.08	†-2.94	39.78†-0.052	†-1.84
F	1126	3358†-15.28	**S.D.**	**Mean**	†-6.34	2.19†-0.08	†-2.81	39.73†-0.051	†-1.72

In the sample, these values were established for all the four variables (Table 2). As is obvious there is considerable difference in the mean birth weight of male infants in relation to female infants, even at the limits of the standard error of the mean, the difference is almost 60 gms. Moreover, there is little difference in the means for material age, parity, and gestation time, as in these three variables the difference is less than the standard errors added together. From this data we can postulate, that maternal age, parity and gestation time being constant, a male infant should be born

heavier than a female infant.

In a survey, where various variables are collected, it is pertinent to try and establish whether or not there is any association between the various groups of variables. E.g. Does gestation time decrease as parity increases, or does birth weight increase as maternal age increases etc? The index of the degree of association between two groups of variables is the correlation coefficient. This index is a value lying somewhere between —1 to +1. A negative coefficient means that as one variable increases the other decreases, while a positive coefficient means that if one variable increases the other increases as well. When the correlation coefficient is O there is absolutely no association between the two variables. As the index is increased the association is more pronounced until a correlation of 1 means that there is absolute dependence between the two variables, i.e. a change in one variable is always accompanied by a relative change in the other variable.

In Table 3 the various correlation coefficiants are listed. From this Table it can be seen that there is quite a good association between parity and maternal age and possibly some very slight correlation between birth weight and gestation time. However, it is possible, that due to the wide variations which can be found in such variables as birth weights, association can be found between two variables with a small correlation coefficient.

Table 3. Correlation Coefficients for Birth Weight, Maternal Age, Parity & Gestation Time.

	Males	Females
Birth weight to gestation time	.330	.356
Gestation time to parity	.003	—.059
Birth weight to parity	.132	.148
Birth weight to mat. age	.093	.135
Gestation time to mat age	—.047	—.079
Parity to maternal age	.626	.675

The means by which these trends can be illustrated are tables and graphs. As an example let us take the mean birth weight and mean gestation time in relation to parity. These mean values are illustrated in Table 4. This table is constructed by finding the mean birth weight and mean gestation

Table 4. Mean Birth Weight and Mean Gestation time for given Parity.

Parity	Weight (gms)				Gestation time (wks)			
	Males		Females		Males		Females	
	No.	Mean	No.	Mean	No.	Mean	No.	Mean
0	431	3346.45	371	3255.58	431	39.85	371	39.86
1	278	3464.24	269	3371.90	278	39.72	269	39.74
2	164	3500.76	145	3403.26	164	39.77	145	39.86
3	111	1519.15	92	3374.55	111	39.68	992	39.45
4	66	3417.91	69	3393.56	66	39.53	69	39.65
5	39	3501.56	47	3406.40	39	39.85	47	39.43
6	37	3611.05	39	3524.26	37	39.62	39	40.05
7	26	3497.15	26	3414.23	26	39.81	26	38.88
8+9	41	3436.80	30	3580.87	41	39.80	30	39.83
10+	39	3792.94	38	3551.87	39	40.10	38	39.45
All	1232	3446.35	1126	3358.49	1232	39.78	1126	39.73

time for each parity. The major limitation of this table is that as the parity increases the number of units decrease so that we are left with very few births in the high parity groups. This could easily give rise to the question of whether the mean values at bottom of the table are truly representative. As a partial counter-measure to this, the higher parities have been grouped together, thus eliminating very small numbers. However, in this table we are still confronted with small groups and therefore great restraint must be exercised in drawing any conclusion. The most that can be said about this table is that despite very gross irregularities it shows a trend for mean weight to increase, as parity increases, while mean gestation time is constant throughout. To have a more reliable table one has to take a larger sample for the higher parities.

A simpler way of showing how two variables behave in relation to each other is by plotting a graph. Thus Table 4 is represented graphically in Fig. 2. The first thing which meets the eye is the irregularity of the graph. Such a graph is confusing and only fulfills its prime object of illustrating any trend, which is present, after careful study. However, by regrouping the various parities it is not only possible to clarify the graph, but also to make it more reliable by increasing the number of units which each mean represents. Fig. 3 is the same as fig. 2 but here the parities have been regrouped. The irregularities registered in fig. 2 have been eliminated and the graph shows that in this sample the mean birth weight tends to increase with parity.

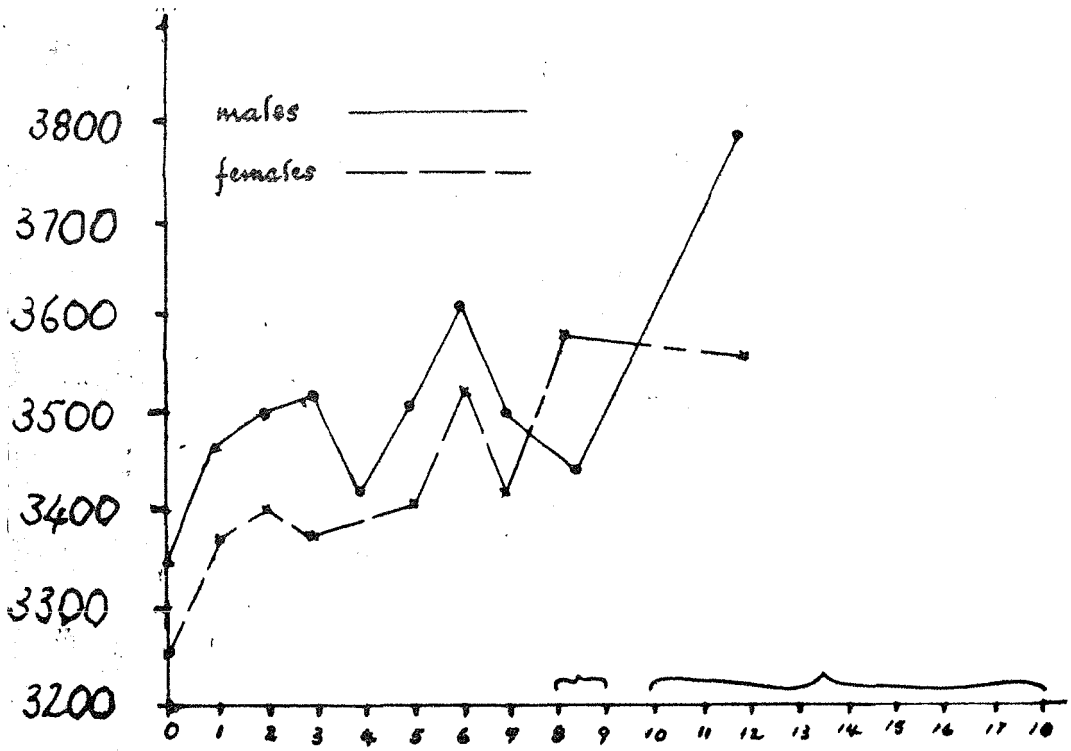


FIG. 2.

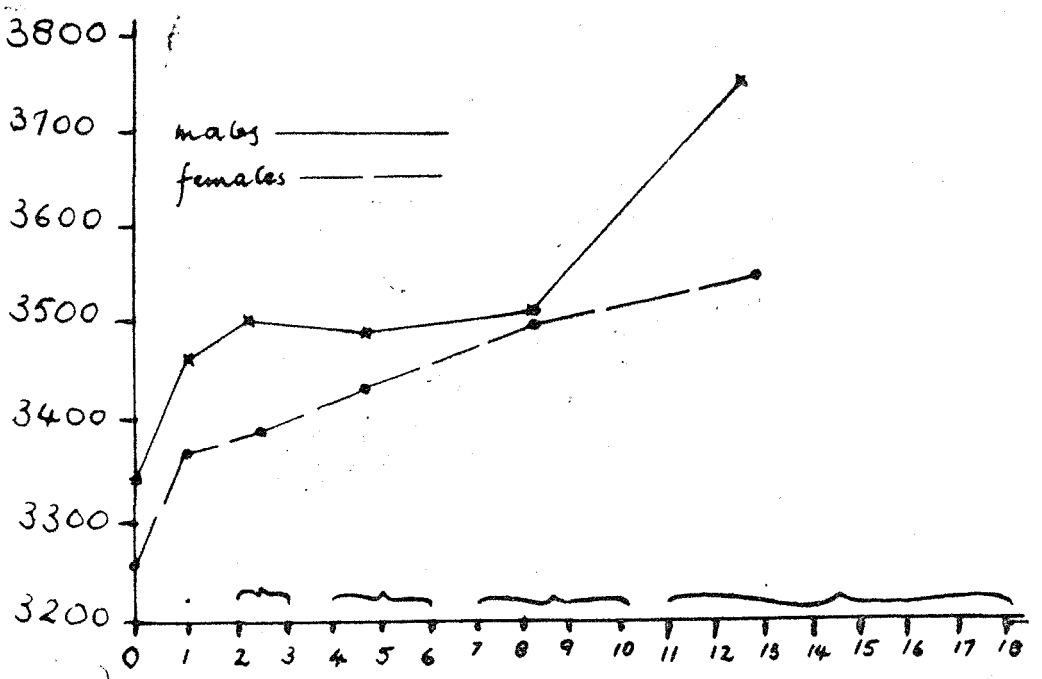
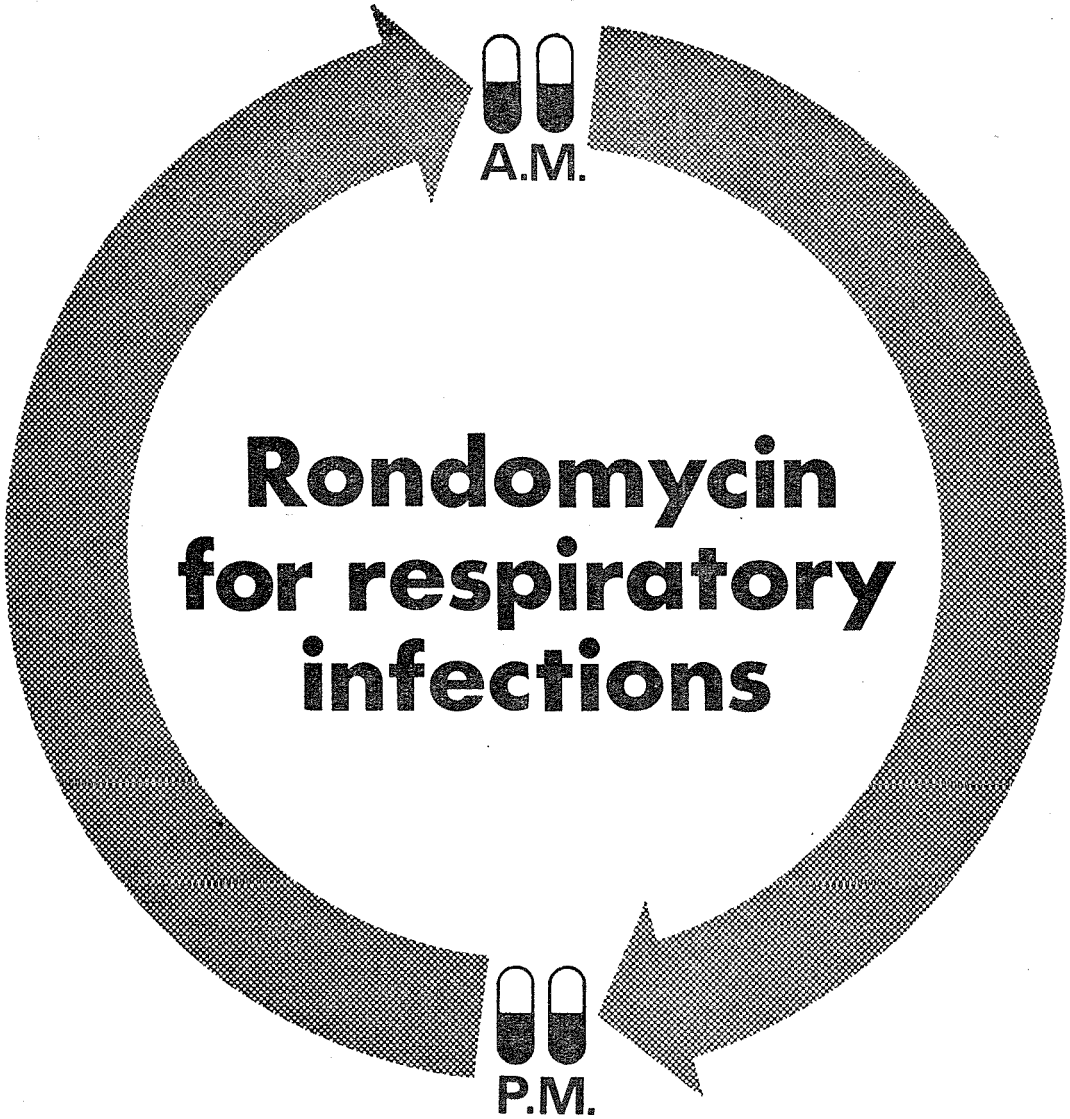


FIG. 3.

Up to now we have agreed with other authors who have published similar studies, but we do not agree in the trend for birth weight to increase in the higher parities. Fraccaro, in an almost identical study, states that it seems that mean birth weight increases with parity up to 8, but above this parity mean birth weight tends to decrease. However, Fraccaro's sample, although larger than this sample has smaller numbers of births above the 8th parity, and as he remarks, no definite conclusion can be based on such a small number of observations.

This controversial point demands further study. Definite evidence is now accumulating that large babies have an increased perinatal morbidity during labour. If by making a more extensive survey, on the relationship between birth weight and parity, it would be shown that the results of this sample are correct, it would partly explain the increased infant morbidity in grand-multiparas.



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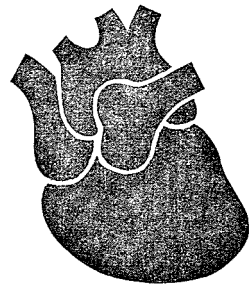
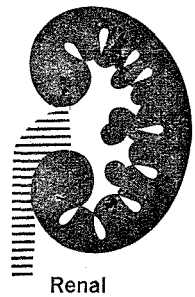
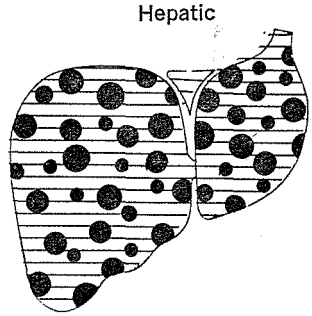


Cardiac



Renal

Hepatic



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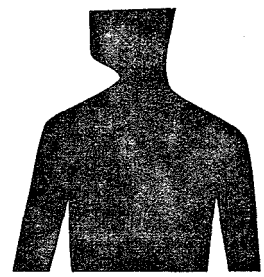

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THE USE AND ABUSE OF ANTICOAGULANTS IN MYOCARDIAL INFARCTION

— *by R. SOLER* —

The wheel has turned a full circle with regard to the place of anticoagulants therapy in the treatment of recent myocardial infarction. Initially therapuetic enthusiasts claimed a marked reduction in the morbidity and mortality rates, especially from thromboemolism, with the result that the use of anticoagulants became widespread throughout the world. With the passage of time enthusiasm had begun to wane; but recent therapuetic trials especially one by the Medical Research Council (M.R.C.) in 1959 has again aquired to a certain degree a prominent place for anticoagulants in the treatment of myocardial infarction.

An understanding of the pathology of myocardial infarction is very helpful in explaining the need for anticoagulants. Cardiac infarction entails necrosis of heart muscle usually due to the interruption of blood supply by coronary artery occlusion. The latter may be due to coronary atheroma with or without supra-added thrombosis. However, cases are recorded where there is no evidence of arterial occlusion at necropsy. In these cases the lumen of the arteries is usually narrowed by atheromatous deposits in the intima. These cases are usually brought about by a disturbance of circulatory dynamics, as occurs in conditions such as shock or severe anaemia. Thus it can be appreciated that infarction does not necessarily imply thrombosis. In cases where the cause of the infarction happens to be arterial insufficiency, anticoagulants will be most helpful in preventing intra-luminal thrombosis of the arteries distal to the site of the infarction and so help in limiting the extension of the infarct which might prove fatal. However, evidence has been brought forward, showing, that anticoagulants can produce extravasation of blood into an atheromatous plaque, and this has been one of the arguments brought against their use in cardiac infarction.

It is agreed that the blood of patients with ischaemic heart disease is hypercoagulable because of the increased thromboplastin generation and increased platelet adhesiveness. Platelet adhesiveness is probably due to a coat of fibrin deposited on the platelets. Since heparin is known to decrease fibrin formation, it consequently reduces platelet adhesiveness. Moreover, has been suggested (Duguid 1955) that atheroma develops as a consequence of fibrin deposition on the intima. Duguid showed that mural thrombi laid down in arteries rapidly become covered with endothelium and may later appear to arise from within the vessel wall. Fat deposition and other changes convert the original lesion into an atheroma. If this hypothesis is correct then one might expect anticoagulant therapy to prevent the extension of the atheromatous process.

Another aspect of thrombotic disease in general which bears a relationship to myocardial infarction, is the physiological process of fibrinolysis. It is known that fibrinogen is continually being converted to fibrin in vivo but that the action of fibrinolysin (or plasmin) prevents the formation of thrombi by a proteolytic action on the fibrin formed. If there is any change in blood coagulation which encourages thrombosis then it might well be that it is the balance between forces for fibrin formation and those for fibrin dissolu-

tion which is the important. Hume (1958) has shown that immediately following an infarct, there is a decreased level of fibrinolysin but this gradually returns to normal levels over the succeeding ten days. Lackner & Mersky (1960) showed that heparin increased the fibrinolytic activity in vivo. This increase in fibrinolytic activity, maximal 1 hour after heparin injection, was frequently observed in patients treated with heparin. It is possible that the action of heparin in promoting fibrinolysis is due to its action on lipids; lipaemia has been proved to inhibit fibrinolysis.

From what has been said so far, it is clear that there is more than meets the eye in the use of anticoagulants for the prevention and the dissolution of thrombi. The pharmacological action of herapin in blood clotting occurs at two main sites. It prevents the interaction of thrombin with fibrinogen to form fibrin and prevents the conversion of prothrombin to thrombin by the blood thromboplastin system. The coumarin derivatives act on the liver and competitively occupy sites on the liver cell intended for the vitamin K which is necessary for the production of prothrombin. Prothrombin depletion in the peripheral blood causes impaired thromboplastin formation and so blood coagulability is reduced.

It has been argued that the use of anticoagulant therapy in acute myocardial infarction is fruitless, because, once the vessel has been occluded by a thrombus, then, the anticoagulants are of no use whatsoever. This statement does not take into account the number of infarcts due to arterial insufficiency as was mentioned above. It must be stressed at the outset that anticoagulant therapy is not curative of the condition but is of prophylactic value in the subsequent few days, following the attack. Thus it is known that retrograde growth of a thrombus may occlude further the coronary vessels and this may be sufficient to cause death from ventricular fibrillation. It may prevent mural thrombus formation in the left ventricle or thrombosis of leg-veins (from stasis of the peripheral circulation due to heart failure following the infarction), with consequent risk of embolisation. Statistics show a reduction in clinically diagnosed episodes of thrombo-embolic incidents.

Myocardial infarction may present in various degrees of severity. In the good risk cases where the prognosis is favourable and the occurrence of thrombo-embolic incidents rare, anticoagulant therapy may be safely omitted and its possible complications particularly haemorrhage avoided. A good risk patient may be considered to be a patient below 60 years, with a first attack of infarction, without history of preceding angina and who shows no major fall in blood pressure following the attack. Other criteria in favour of a 'good risk' case are the absence of cardiac failure or arrhythmias; no history of diabetes mellitus or other sign of previous arterial disease elsewhere, and in a patient who is not obese. If these criteria are fulfilled it may be fairly said that the possible complications of anticoagulant therapy far outweigh the risk of thrombo-embolic incidents. Moreover in patients with coronary artery disease of sufficient severity as to have caused a previous recognisable infarct, long term anticoagulant therapy can only make a limited type of contribution in terms of reduction in deaths and reinfarction rate. Naturally this long term anticoagulant treatment does not make a therapeutic attack on the fundamental aetiology of mycoardial infarction, but merely interrupts one of the terminal links in the chain of events leading to this lession. From the statistical evidence (which is discussed later (M.R.C.) it was found that the benefits of long term treatment were greater in angina cases than in those who had already suffered an infarction, suggesting that the earlier the disease is so treated the greater is the benefit. Moreover it was noted that in the older age group and in patients who had already suffered one or more infarcts, the contribution made by therapy was unsatisfactory.

On the other hand, the patient himself may present definite contra-indications of anticoagulant therapy of

any sort. Thus a patient, who is judged to lack sufficient intelligence to carry out the treatment or who is unreliable in attendence to the out-patient clinic, is not a fit candidate for long term anti-coagulant treatment. A patient who is a chronic alcoholic or suffers from liver dysfunction may provide a greater risk to bleeding due to the deficient prothrombin formation. A patient with an active peptic ulcer, hiatus hernia or other lesion of the gastro-intestinal tract known liable to bleed should be excluded from anticoagulants. Malignant hypertension associated with hypertensive retinopathy or any retinopathy (diabetic, renal), in which there is evidence of fundal haemorrhage, constitute other contraindications. A raised blood urea or surgical lesions of the kidney (calculus) should also be borne in mind when anticoagulant therapy is being contempalted. A patient with a known blood dyscrazia should also be eliminated from anticoagulant therapy. Finally pregnant or nursing mothers should also be taken off the list of patients for anticoagulants. Certainly the availability of a well-equipped laboratory for the necessary prothrombin and clotting time determinations is essential. From the preceding list of conditions it can be seen that the major hazard of anticoagulants is the liability to haemorrhage. However the statistical evidence does not present such a gloomy picture as one might think. Haemorrhages of a minor degree are two or 3 times as common as the casastrophic major incidents e.g. haemoptysis or haematemesis. With short term therapy, that is up to 4-6 weeks the incidence of haemorrhage is roughly 5% of cases treated. The incidence of bleeding during long term therapy is of the order of one case per 7 treatment years (M.R.C. 1959). It will be noted that the incidence of bleeding is higher in the former than in the latter. This fact can be explained by application of therapy to a case, which constitutes one the contraindications mentioned above; thus for example the development of a major haemorrhage bringing to notice an unsuspected peptic ulcer. Naturally such cases should be excluded from anticoagulant therapy. Besides this danger from bleeding, long term therapy with phenindione is liable to produce other distressing side-effects of which a sensitivity reaction is the most important. This allergic reaction takes the form of a rash accompanied by pyrexia and leucopenia. Progression to exfoliate dermatitis can occur. Other less common side-effects are serious renal damage with albuminuria, anaemia and a leukomoid blood pictures, diarrhoea, and disturbances of vision. Any signs of the development of side-effects naturally precludes the cessation of treatment. As judged by the M.R.C. trial sensitivity reactions occurred in 1.5% of patients and of the three fatalities recorded, one was attributed to agranulocytosis and the other two to a renal lesion.

The rationale behind the use of anticoagulants as an adjuvant to standard treatment of a myocardial infarct, is to prevent the extension of the original thrombus, which has caused the infarction and therefore prevent the extensin of the damage; to prevent a fresh myocardial infarct, and finally to reduce the incidence of thromboembolic episodes.

Usual sequalae of an infarct, after the preliminary state of shock has passed off, is the development of atrial fibrillation and of mural thrombi in the left ventricle subjacent to the area of infarction. Emboli shot off from the atrium of ventricle can lodge in the cerebral vessels or in any systemic artery. Pulmonary embolism from peripheral venous thrombosis, usually from the leg, is a major hazard.

Anticoagulant therapy can be instituted on a short or a long term policy. The evidence in favour of a short term anticoagulant therapy is not so favourable; even so, due to lowered mortality rate in long term anticoagulant therapy, it should be started as soon as the patient is admitted to hospital on the basis that long term therapy is likely to be obligatory. Honey and Truelove (1957) concluded that such a reduction in mortality as occurred in anticoagulated patients was

due to a lowering of the incidence of fatal pulmonary embolism. Certain physicians are still, however, hesitant in giving anticoagulants to all patients admitted with myocardial infarct; so they take the middle road and reserve treatment for patients in whom the prognosis is poor. The 'poor risk' patients, about 30% of those admitted for myocardial infarction, are considered to be those who have had a previous infarct and who suffer from shock; those with heart failure, or atrial fibrillation and flutter or a bundle branch block; and those who show signs of ventricular anuerysm, severe diabetes, thrombophlebitis, and those who are markedly obese.

The statistical evidence so far brought forward has shown that the only type of anticoagulant therapy which can claim a certain amount of success is the 'long term' treatment. Therefore, if it is decided to embark on anticoagulant, it will be of greater prognotical value if one were to adopt the long term regime. At the beginning of this paper it was stated that treatment with anticoagulants is again coming in favour with many practising physicians. How has this change of opinion been brought about? There have been three well constituted clinical trials or long term anticoagulant therapy in the last ten years. These have shown a definite improvement in prognosis in patients suffering from myocardial infarction. These trials were conducted by Bjerklund and Borchgnevink in 1957 and 1960 respectively and by the Medical Research Council in 1959 with a follow-up in 1960. May I here be permitted to digress a bit from the subject matter and say that M.R.C. report was the paper which stimulated my interest in this highly controversial subject. Whilst agreeing to the fact that some of the criticisms on the available trials are admissible, these criticisms do not in their own right completely invalidate the evidence in favour of anticoagulants. Indeed, unless a properly constituted trial should be conducted which disproves the alledged benefit, then the existing claims for its use in acute myocardial infarction must be accepted.

I propose to deal with the M.R.C. trial in a certain detail. The purpose of the trial was to determine whether, in patients who had survived at least one month after their most recent infarction, continuous anticoagulant therapy would reduce the risk of recurrence and death below the levels concurrently observed in a series of comparable patients not so treated.

Only patients with the Q wave electrocardiographic evidence of recent infact were included. The age of the patients admitted was from 40 to 69 of either sex and they were admitted to the trial at any stage from the 29th day to the 42nd day after their recent evidence of infarction. Patients who showed any of the following conditions were excluded from the trial.

a) Haemorrhage from any site within the previous 6 months.

b) Peptic ulcer on clinical or radiological diagnosis.

c) Any lesion thought likely to bleed.

d) Hepatic disease.

e) Renal disease with persistent raised blood urea.

f) Malignant hypertension.

g) Cardiac failure.

h) Previous cerebrovascular accident.

These in fact, constitue the contra-indications which were mentioned above.

The judgement on the benefit or otherwise of this therapy rests on two criteria viz. the death rate and the reinfarction rate. In the M.R.C. trial 165 patients (males) received anticoagulants and 100 patients acted as a control group receiving placebos. Of this number of patients, the deaths recorded amounted to 17 in the first group and 28 in the control group. There are some critics who are unwilling to accept the reinfarction group as valid evidence because the adjucating clinician was aware of those in

the treatment group. In the M.R.C. trial there were 17 patients with a recurrent infarction in the treatment group and 54 reinfarction incidents in the control. If these figures are given as percentages, it will be found that 20% of patients receiving anticoagulants either died or suffered from reinfarction whilst 51.3% of patients in the control group suffered from the same result. These figures suggest that there is a marked reduction in mortality and reinfarction rate in patients receiving anticoaguants than in those not so treated. It must be stressed again that the evidence in favour of long term anticoagulants is still statistical.

There is some evidence that therapy is more effective in the under 55 age group. The death rate was reduced by 50% in those under 55 years and by 33% in those over 55 years whilst the reinfarction rate in those under 55 years was 20% as compared to the 50% incidence in patients over 55 years. The deaths occurring in the test group was maximal during the first 3 to 6 months and it has been suggested that this increase in relapses during the early part of the follow-up was due to early cessation of treatment. The major cause of death in both the control and the test of groups was recurrent infarction which suggests that although anticoagulant therapy reduces the mortality rate it does not entirely prevent recurrent infarction; it does however reduce the incidence of embolism, since only one case of death was attributed to cerebral embolism in the M.R.C. trial and this occurred in the control group. On the other hand although much fuss is made about the risks of haemorrhage in using anticoagulants, the incidence of bleeding severe enough to cause death amounted to one in the treatment group. Hence, barring the presence of any lesion liable to bleed, the dangers of therapy are small indeed as long as proper check is kept on the blood prothrombin time.

The regime of treatment varies from clinician to clinician. However, they all, more or less, follow the form outlined below.

10,000 units of heparin are given intravenously every 3 hours for the first 48 hours. An oral anticoagulant, Phenindione, is started concurrently with heparin. 200mg of phenindione should be given on the first day, 150 mg on the second day and 100 mg on the third day. After 48 hours a prothrombin time is carried out. The ideal anticoagulant effect is two to three times the nomal (16 secs.) prothrombin time. The maintenance dose of phenindione can then be gauged from assessment of the initial prothrombin time. If the above regime is carried out the maintenance dose works out to be 100mg to 50mg daily.

In the short term therapy, anticoagulants are continued as long as the patient remains in bed. However, as has already been stressed, the patient is better safe guarded against reinfarction if he is put on a long term policy. Certain precautions are required if the patient is put on long-term therapy. The patient should be kept as an outpatient and regular check is kept on his prothrombin time. He should be warned not to undergo any surgical procedures, especially tooth extraction without prior consultation with the physician in charge of his treatment. He should be warned against partaking of such drugs as salicylates, cincophen phenylbutazone, oral antibiotics and ACTH all of which tend to precipitate bleeding. If after a number of years it is thought fit to stop treatment then it will be good clinical practise to taper off the dose over a 4 week period by reducing a quarter of the stabilising dose each week. This precaution is essential to avoid the rebound hypercoagulabiliay of the blood which occurs when anticoagulants are stopped suddenly and which might easily result in a recurrent thrombosis.

If inspite of all the precautions undertaken, haemorrhage develops, 5 ml. of a 1% protamine sulphate solution are injected slowly intravenously if the patient is on heparin or if he is on oral anticoagulants, the drugs should be stopped and vitamin K, 100

to 50mg, are injected intravenously. Blood transfusion should be given in all cases until the effect of oral anticoagulants wears off.

The role of anticoagulants in myocardial infarction is still undecided. From the study of the extensive literature on the subject, I have reached the conclusion that there is a place for anticoagulants in certain special cases, that is the poor risk patient mentioned above. However, one should not be dogmatic about their use, as quite a substantial number of cases present definite contra-indications to their use. On one point is there agreement among all clinicians and in that, anticoagulants are a *must* in preinfarction angina. Until our diagnostic procedures are improved to bring to light these patients before the catastrophy and the layman instructed to present to the clinician earlier, the use of anticoagulants in the established case will remain an illdefined prophylactic against re-infarction.

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THE DEVELOPMENT OF MEDICAL JURISDICTION

— *by M. NARRAINEN.* —

Medical Jurisdiction of Forensic Medicine may be defined as the application of medical and para-medical sciences to the purposes of the law, both civil and criminal, and the adminsteration of justice.

The emergence of Medical Jurisprudence, as a separate scientific entity, depends upon the existence of a legal system and a body of Medical knowledge. Its history and development can only be traced from a stage of civilization when records became available. The earliest records take us back only about five thousand years.

Medicine and Law in Egypt.

The early civilizations of the Near East and those of the Nile Valley have left ancient inscriptions and papyri which give us some idea of the state of knowledge. There is no doubt that there was an extensive and fairly well systematized knowledge of medicine, and that the approach to medical matters was scientific to some extent. This is evident from the numerous medical papyri including Kahun (gynaecological) 1900 B.C., Edwin Smith (surgical) 1600 B.C., Ebess (medical) 1550 B.C.

The papyri, the illustrative stone inscriptions, and the mummies, form an excellent picture depicting Egyptian law and medicine from 2500 B.C. onwards. There was in existence a definite system of laws relating to crime, property, marriage and other civil matters. Depending on the severity of the crime, the convicted person received punishment. This varied from a few strokes with a lash, torture, mutilation, or forced labour, to being thrown to the crocodiles of the Nile.

In medicine, both magic and mysticism coexisted with sound medical knowledge. The practice of medicine was controlled by special regulations. The physician's position in the social system and in the state was clearly defined. Only members of a certain class were entitled to practise medicine, and physicians enjoyed privileges usually accorded to more eminent ranks. Any physician, acting contrary to laws from the sacred books, was condemned to death.

There were specialists in all branches of medicine and surgery: "some are for the head, others for the eyes, others for the teeth, others for the intestines, and others for intestinal disorders". The knowledge of drugs, including metallic and vegetable poisons was considerable. Salaries were paid by the State Treasury.

The development of regulations continued gradually, possibly from the precepts of Imhotep and his followers.

Imhotep (signifying "he who cometh in peace", 3000 B.C.) was Chief Justice, Grand Vizier, astronomer, physician and architect to King Zoser. He combined the sciences of law and medicine and he rightly deserved to be called the first medico-legal expert. Unfortunately, Imhotep whose cult preceeded that of Aescalepius, was worshipped as a divine god. Egyptian medicine was weakened by the dead-weight of traditions mingled with magic and divinity. Charmes, amulets and incantations were used to drive away evils inhabiting the body. Orthodoxy won the day, and no physician departed from "established" traditions. Apart from the extensive knowledge of drugs and poisons required, and the examination of cadavers to ascertain the cause of death, there is no other evidence of medico-legal practice.

Sumerian and Oriental contributions.

In Babylonia and Asyria: Practice of

medicine was entrusted to a special caste, and was rigidly controlled. Although medicine was dominated by magic and sourcery, it was eventually organized, and reached the stage of Egyptian medicine.

From the code of Hammurali (2250 B.C.), the physicians were rewarded with adequate fees as prescribed and regulated by law. But if the doctor caused the patient to lose his life or his eye, he had his hands cut off in the case of a gentleman, or he would have to render value for value in the case of a slave.

In Persia: Disease was regarded as possession by the devil, while medicine and surgery were thought to be derived from god. Incest, sexual vice and perversions were punishable offences. The competence of the medical practitioner was ascertained by practising upon heretics: "if all three died in succession, he was regarded as unfit; the loss of another became premedicated murder; if all three recovered, he was admitted to practice."

Jewish medical Laws.

The principal sources are the Bible and the Tahmud (the law as transmitted by verbal tradition with interpretation and commentaries). The medical practitioner was highly esteemed as reflected by the impressive language of Jesus, son of Sirach (1800 B.C.):

(1) "Honour a physician according to thy need of him, with the honours due unto him: for verily the Lord hath created Him".

(11) "The skill of the physician shall lift up his head: and in the sight of great men he shall be admired".

The Mosaic mandates against bestiality, sexual inversion, and the investigation to be made in the case of disputed virginity, point towards the beginning of medical jurisprudence.

India: The right to practice medicine was restricted to Brahmin priests and scholars, and a prescribed method of medical education was enforced. By law, girls under the age of twelve could not marry; the duration of pregnancy was taken to be between 9 and 12 lunar months. Special attention was paid to poisons and antidotes, and it was also considered essential to distinguish between various poisons.

So far we have not yet seen the establishment of forensic medicine as a science, but the basis is being laid down in the form of laws regulating medical education, admission to the profession, ethics and toxicology.

China: A remarkable work of the Sung dynasty, (1280 A.D.), is; "HSI YUAN LU" or instructions to coroners. It was compiled between 1241-43, and it includes proceedure for investigatting deaths in suspicious or alleged criminal cases. This very interesting document contains minute directions for the proper examination of wounds on a body, and also indicated the sites where a wound is likely to be mortal. A systematic examination from the head downwards is stressed, irrespective of the state of decomposition of the body. The examiner is warned against faked wounds. The document deals with wounds caused in various methods, e.g. blows from the fist, kicks or weapon wounds. Death by strangulation, suicide, drowning, and poisoning are equally described. The possibility of confusion between antemortem and postmortem bruising, and the passing off of homicidal strangulation for suicide is clearly recognized. Toxicology was also given considerable importance. The examiner is put on his guard for many possible eventualities. He is even advised to examine the locus. We are drawn to the conclusion that medical jurisprudence in Ancient China was fairly well developed and reached an advanced stage, as compared to medieval European practice.

Greece: Before this stage of civilisation, medicine was mainly instinctive, empirical, magical and, in spite of the high degree of practical knowledge and technical perfection, it was applied mainly with the immediate purpose of stopping pains or prolonging

life. Hippocrates (460-370 B.C.) gave Greek medicine its scientific outlook, spirit and ethical ideas.

Hippocrates and others considered many medico-legal problems, e.g. fatality of wounds in different parts of the body, duration of pregnancy, viability of children born before term, superfoetation, malingering. Evidence is lacking to show whether such issues ever came before the courts. The Greek legal system, including its criminal procedure, was very comprehensive and it is likely that the opinions of her famous physicians were sought.

The text of the Hippocratic oath is a shining example of the ethical rights which the concept of professional parctice had reached in early times. The oath included an undertaking not to give deadly medicines (poisons) to anyone if asked, nor to suggest such a course; not to assist in procuring abortion; not to seduce females or males in any house the physician enters and not to divulge anything seen or heard. The substance and spirit of the oath still governs the whole ethical outlook of the medical profession.

Rome: Before the establishment of Greek medicine in Rome, laws, relating to malpraxis, poisoning, and fraudulent manipulation of wills, were non-existent. Medicine made great progress during the course of the Empire. Both Greek and Roman physician helped in advancing the objective approach to medicine, among whom were Celsus (4 cardinal signs of inflamation; calor, dolor, rubor, tumor), Galen (who added the fifth sign: functio laesa), Dioscorides, Rufus, Soranus, Antgelus.

It is not known to what extent the courts made use of medical evidence, but cases have been recorded to show that medical evidence was submitted. For example the physician, who examined the assasinated body of Julius Ceasar (44 B.C.), was of the opinion that of all the 23 wounds, only one, penetrating the chest was of a fatal nature. In Hadrian's rule the legitimacy of births after abnormally prolonged pregnancies was held, as it was considered by the physicians, that no fixed maximum period of gestation could be stated with certainty.

Rome's contributions to medicine lay not only in the realms of hygeine and public health, but also in forensic medicine. Justinian legislation may be said to have given shape to medical jurisprudence. The inactments offered between 528 and 564 A.D. and its essential features have been incorporated in many legal systems. The code regulated the practice of medicine, surgery and gynacology and clearly recognized the medical profession, with the necessary educational requirements, and competent standards. The number of physicians in each town was limited, and the penalties for malpraxis were prescribed. The medical expert was required to assist the court by this expert knowledge and opinion rather than appearing for one side or the other: "Medici non sunt proprie testes sed majus est judicium quam testimonium."

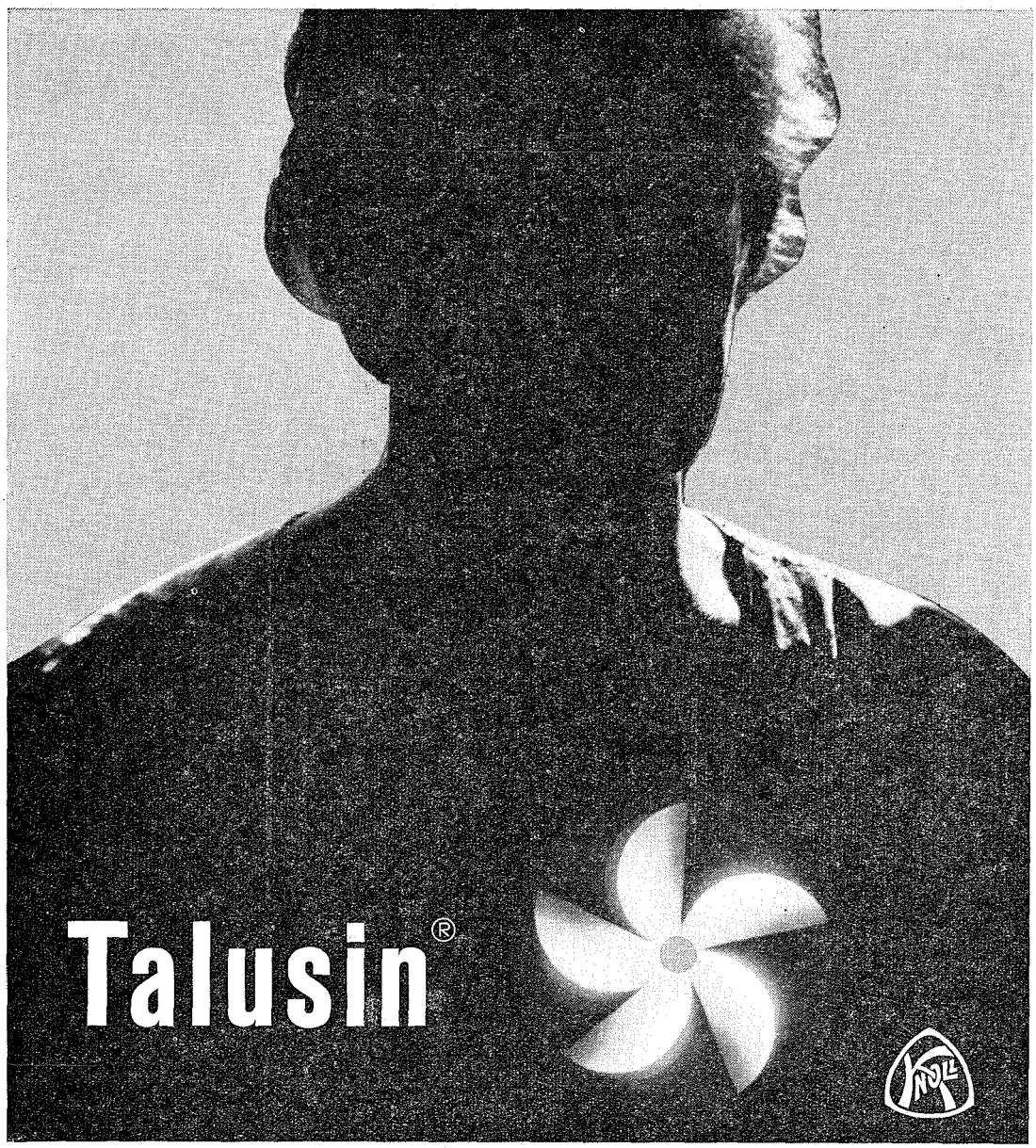
We see that the status of medical expert is established by law and his opinions were required in civil and criminal proceedings; e.g. in the determination of pregnancy, impotence or legitimacy, in cases of rape and poisoning, in matters relating to wills (testamentary capacity and survivorship).

After the fall of the Roman Empire, medicine became stagnant and the scientific approach gave way to tradition and authority. Legal proceedure was very crude. Trial was by ordeal, and confessions were obtained by torture. Expert opinions given were of the nature of hair-splitting casuistry.

There is no evidence of progress in forensic medicine, until the sixteenth century.

RENAISSANCE

During this period of awakening from intellectual lethargy, the earliest German text of medical jurisprudence of consequence is the "Constitutio Criminalis Casolina", issued by Emperor Charles V, in 1553. This text is based on certain laws issued by the Bishop



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of Bamberg in 1507, and by the Elector of Brandenburg in 1516.

For the first time in the development of medical jurisprudence, the judge was empowered to summon physicians and midwives as expert witnesses in medico-legal cases, such as homicide, infanticide, criminal abortion, wounding, poisoning, hanging, drowning, malpractice. No post-mortem was authorized.

This progressive tendency spread to other parts of Europe. Medicine was abandoning Galenism, and great improvement in its practice was noted. In 1511, the English act decreed that no one should practice medicine or surgery in London, or 7 miles around, unless examined, approved and admitted. By the 1522 and 1553 acts, the forerunner of the Royal College of Physicians of England was founded, and the "statutes" constituted one of the earliest and most important examples of a local code of ethics.

Towards the end of the second half of the 16th century, Ambroise Paré (1510-1590), the French army surgeon, published his treatise on medical jurisprudence (1575) which included methods to be adopted in the preparation of medico-legal reports. He also wrote on carbon-monoxide poisoning in 1575, and gun-shot wounds in 1545. It must be remembered that Paré performed the first judicial post-mortem in France, in 1562.

Age of intense individualism.

In the 17th century, the age of Harvey, Newton, Galileo, Copernicus and Gilbert, and Italian physician Fortunato Fidele (1550-1630), who was a better known investigator than his predecessor Battista Codronchi, published a great work entitled "De Relationes Medicorum", (Palermo 1602).

This treatise dealt with the attestation of Virginity and time of delivery, the jurisprudence of poison, lethal wounds, hereditary disease, torture, and monsters.

Another Italian, Paolo Zacchia, (1584-1659), physician to Pope Innocent X, surpassed Fidele by his impressive work: "Quaertians Medico-legals" (Rome 1621-35), consisting of 3 volumes. The first volume dealt with age, legitimacy, pregnancy, superfoetation, death during delivery, resemblance of children to their parents, the jurisprudence of insanity, poisoning, impotence, malingering, virginity, rape, wounds, mutilation, miracles, plague, contagion, and salubrity of the air.

The second volume introduced various problems, which were discussed in the light of medical and legal authority. The third volume contained cases (consilia) with the sephia and decisions of the courts.

In spite of its shortcomings, his work was regarded as a classic text through Europe. However, although Fidele and Zacchia have prepared the way for the further progress of legal medicine, Italy did not keep the lead, and lapsed into a non-progressive state.

In France, the works of Nicolai de Bligny (1684), and Devereux (1694), followed those of Ambroise Paré.

New discoveries were made in anatomy and physiology, and in 1628 Harvey proved the circulation of the blood in the body. A subject on which Harvey remarked, i.e. the difference between the lungs of a foetus and those of a breathing infant, was helped by Swammerdam's discovery of the Hydrostatic test (Tractus de Respiratione, Leiden 1662). In 1682 it was applied in a legal case by J. Schreyer.

Birth of Modern Medical Jurisprudence

The 18th century, the age of Hunters, Hales, Morgagni and Jenner, was also the age of theorists and system-makers. Germany soon followed Italy's lead with the work of Saevus, J.F. Pfeiffer, G. Welsch and Johann Bohn (1640-1718). Bohn, a professor of anatomy and a physician,, was one of the first to start instruction in Leipzig, and he published his first work on lethal wounds in 1689. He gave exact directions for the autopsy proceedure and insisted that all cavities of the body be opened in medico-legal necropsies. His comprehensive treatise: "De Offic-

io Medici Duplici Clinici Niminum ae forensis" was published in 1704.

Medical Jurisprudence which had hitherto been a part of state medicine and public health, was carefully systematized in the 18th century, in which field the Germans lead, and were the first to found professorships in forensic medicine. Many important works were published by German writers, and and the earliest to rival Zaceline's "Quartiares Legales", was "Corpus Juris Medico Lejale" — 1722, by Machael Bernhard Valentine (1657-1729) of Giesseu. In 1723 H.F. Teichmayer published "The Institutians", a standard authority for a long time and Michael Alberto wrote a six volume work, system, in 1736-47.

The Germans were publishing cases in increasing numbers. These helped greatly in defining the issues, and suggested the best methods to solve them.

In France, Antoine Louis (1723-92), the first systematic teacher of medical jurisprudence, applied medical knowledge to court-room practice. His memoires appearing in 1763, dealt with the differential signs of murder and suicide in cases of hanging and drowning. In 1764, in the Villebranche case, he tried to set the time limits of normal gestation which was fixed ultimately at three hundred days under the Code Napoleon as in Roman laws of the twelve Fables. Lafosse described the positive signs of pregnancy and parturition and investigated and distinguished ante-mortem from post-mortem phenomena.

In 1789, Chaussier emphasized the importance of forensic medicine and started a course of lectures to students. Three chairs of legal medicine were established in Paris, Montpellier and Strasbourg.

Francois-Emmanuel Fodisé (1764-1835) published in 1796 his "Traité de Mèdicine Lègale et Hygiéne Publique", and in 1798, he won the title of the Nestor of legal medicine by his work "Les Lois Eclaisées par les Sciences Physiques".

Medical Jurisprudence in G. Britain.

Britain entered the field of medical jurisprudence during the age of scientific medicine. Both British and continental discoveries have become part of the body of accepted medical knowledge. Anatomy and physiology were fairly well developed and a microscope had been in use for almost a century. Many new scientific and medical societies had come into existence.

The laws of the continent and of Britain were quite comprehensive and embodied in substance the fundamental principles for the function of a medico-legal science. Before the establishment of forensic medicine or its teaching in Britain, medical evidence was given and accepted in the courts. Many famous medico-legal cases have been recorded n the 17th and 18th centuries e.g. in the trial of the alleged murder of Sir Edmund Godfrey, two surgeons gave evidence as to the time of death and the type of injury that caused his death. Another famous trial of the 1t8h century, was that of Eugene Aram in 1758. He murdered a man, Clark by name, 13 years previously. Certain bones alleged to be those of Clark, were found, and medical testimony had to estabish the identification of these bones. The bones were identified as belonging to a male of the same stature and age as Clark, and it was concluded that death was due to a deadly blow on the base of the skull. Aram was convicted of murder and sentenced to death.

Wlliaim Hunter's essay in 1783 on the signs of murder in bastard children is probably the most important contribution. In 1788, Dr. Samuel Farr (1741-95) published his influential volume entitled "Elements of Medical Jurisprudence".

The following year in Edinburgh, Andrew Duncan (1744-1828) was appointed Professor of Medicine in the University and he began a course of lectures in public hygiene and medical jurisprudence, thus becoming the counterpart of Chaussier in Britain. He stressed the importance and extent of medical jurisprudence as a branch of Education. In 1781, noticing the shortcomings of medical evidence in criminal trals, Andrew Duncun was impress-

ed by the inability of John Hunter to answer a simple important question put to him by a judge in a case of poisoning. Through his repeated efforts, the First British chair of medical jurisprudence was instituted by the Crown in 1807. This creation met with adverse criticisms and even opposition in the House of Commons. His son became the first professor in 1807.

Interest in medical jurisprudence was aroused throughout Britain. In 1866, the first book on forensic medicine by Dr. Male, of Birmingham, was published. Courses of lectures were started in the old Medical Theatre of Windmill Street; in the anatomical theatre at Southwest; and in the Universty of London, and in the Westminister Hospital. In 1821, Dr. J. Gordn Smith, of the Westminister Hospital, published his work: "Principles of Forensic Medicine", as applied to British Practice.

In 1819, Andrew Duncan, seconder, was succeeded by Professor William Pulteney Alison. In 1822, Sir Robert Christisan (1797-1882) became Professor of Medical jurisprudence. His work on oxalic acid, lead and arsenic poisoning is well known. As famous toxicologist he published his 'Treatise on Poisons', in relation to Medical Jurisprudence, Physiology, and Practice of Physic. He was a medico-legal adviser to the Crown in many famous criminal trials including the Barke and Hare murders. He also wrote excellent articles on asphyxia and bruising.

Professor Christisan was appointed Professor of materia medica in 1832 and Thomas Stewart Traill succeeded him.

In Glasgow, a chair was institued, and Robert Cowan became professor. In 1841, Dr. Harry Raing succeeded him, until 1872. In Aberdeen, Francis Ogston was lecturing on legal medicine in 1839 and became professor in 1857.

In London, in 1821, Dr. Michael Ryan began a course of lectures at the Westminister Hospital, and in 1831, he published his "Manual of Medical Jurisprudence and State Medicine" based on Continental and British authorities.

In 1834, Alfred Swaine Taylor was appointed Professor of medical jurisprudence at Guy's Hospital medical school, and he published his edition "Elements of Medical Jurisprudence" in 1836. His work, "Poisons", was published in 1848, and his famous "Principles and Practices of Medical Jurisprudence" in 1865. In 1844. King's College appointed a Professor of forensic medicine.

Sir Bernard Henry Spilbury (born in 1879), lectured in forensic medicine at St. Bartholemew's Hospital.

Further Progress in Medico-Legal Study

With the wider development of medical jurisprudence, both medical and paramedical sciences are applied to legal requirements. The chemical recognition of poisons in the victim's body, blood stains, investigations by microsccpic and serological tests, blood groupings in cases of suspected paternity, the microscopic identification of semen and other fluids and the incriminating bullet in gun shot wounds, are some of the special tests that have revolutionised the standards of medical evidence and opinions.

In France, Fodarè published his greatest work in 6 volumes, covering evry aspect of forensic medicine and public health.

Orfila, a Spaniard, graduated in medicine in Paris in 1811, and later became Professor of Legal Medicine in that city.

In 1814, the first edition of his "Treatise on Poisons" was published. Among his man pupils was Robert Christisan of Edinburgh. Besides being accomplished in Texicology, he was an all-rounder, and his "Lecons de Mèdicine Légale" appeared in 1821, as a very comprehensive work. Other contemporaries of Orfila were; Lecieux, Renard, and Devergie.

In Germany, more professional chairs were created, and their occupants contributed to both the scientific and practical development of the subject. In the Berlin School, Johann Ludling Caspar (1796-1864) achieved a reputation through his works on medical statistics and state medicine, judicial post-mortems, and his "Practical Handwork of Legal Medicine" (1856) which remain-

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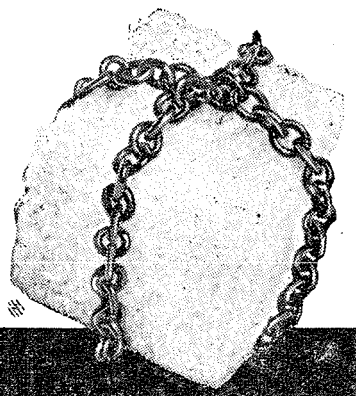

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ed, for a long time, unsurpassed for its wealth of facts and sound judgements.

Forensic medicine was widely established in Britain and Europe by 1950. Medical evidence was becoming very precise and valuable, and its march forward is being continued by eminent medico-legal workers in many parts of the world.

Medical Jurisprudence in America

In the United States, progress has not been uniform. A good start was made in 1813, by the appointment of Dr. J.R. Stringham as Professor of medical jurisprudence. Dr. Stringham being a graduate of Edinburgh, was influenced by the teaching of the Duncans. Other medical schools quickly included a course of lectures in their curricula. Dr. T. Romeyn Beck (1796-1855) was appointed lecturer in 1815 at the western Medical College, New York State. In 1823, he published his "Elements of Medical Jurisprudence", the best American work in its day running through ten editions and many translations.

Isaac Ray (1807-1881), of Beverley, Massachusetts, wrote his first treatise on medical jurisprudence of insanity, (1838).

Unfortunately, the high hopes entertained about American jurisprudence had not been fulfilled, as seen by the criticisms of Professor Stanford Eullson Chaille in 1876. Considerable improvements have resulted within the present century.

Many states have competent medical examiners, to whom medico-legal cases are referred, and medical jurisprudence is now receiving greater attention in many medical schools.

Well known names like Martland, Helpem Leary, and others, are included among modern American authorities.

In Latin America, forensic medicine as a university subject is further advanced than in the United States.

The European systems of establishing claims, is generally accepted at the University.

Scope of Medical Jurisprudence

Forensic medicine through its historical travel from magic to modern science, has established itself as a separate entity after divorcing Public Health, and obtaining relief from physchiatry.

It has attained a high degree of specialisation within itself, and most countries have found it necessary to establish institutes of legal medicine to coordinate the work of the specialists. The forensic expert is continually being faced with problems arising from the needs and complexities of modern industrial societies, and quite often he has to enlist the cooperation of experts in various scientific fields.

Apart from the scientific detection of crimes, the prevention of criminal negligence, and loss of life, the doctor should be quite conversant with the medico-legal aspects of the practice of medicine as the public, in becoming increasingly aware of its legal rights.

In recent years, most medical schools have felt the urgent need of including forensic medicine in the medical curriculum. This wise step has greatly helped to enhance the further development of medical jurisprudence.

Acknowledgement has been made throughout this article to a number of works, but I am very much indebted to the following Histories of Medicine:—

"A short history of Medicine", by C. Singer.

"A History of Medicine", by D. Guthri

"A History Medicine", by A. Certighioni.

'Medical History from Earliest Times' by E.T. Worthington.

"An Introduction to the History of Medicine", by F.H. Garrison.

'The Source Book of Medical History' by S. Cleudenming.

'Etude Historique sur la Responsabilite Medicale" by H.E. Hillairet.

"History of American Medicine", by F. Marti-Ibanez.

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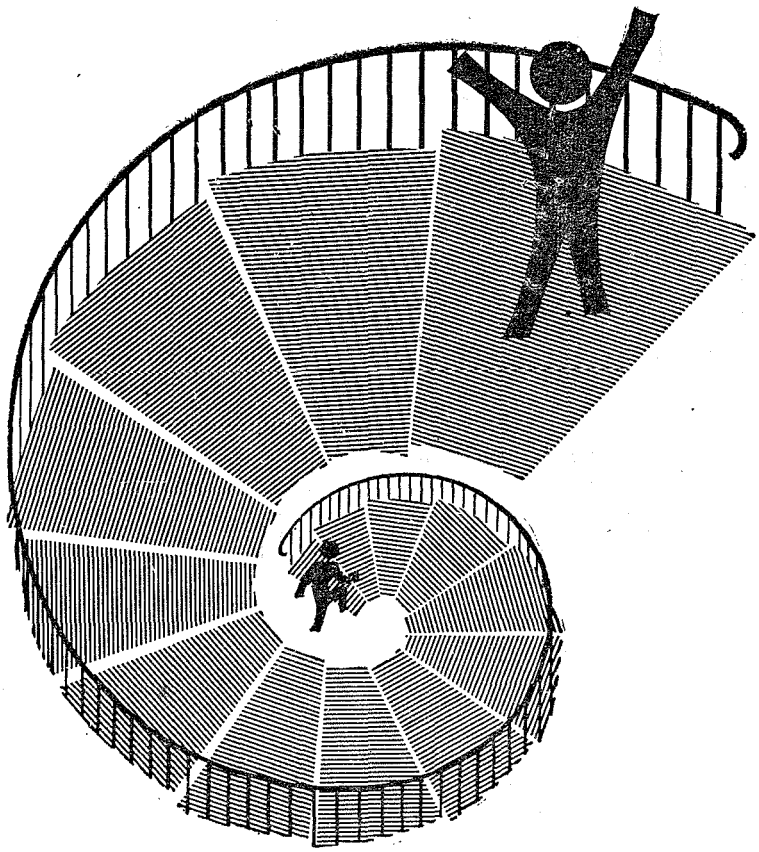

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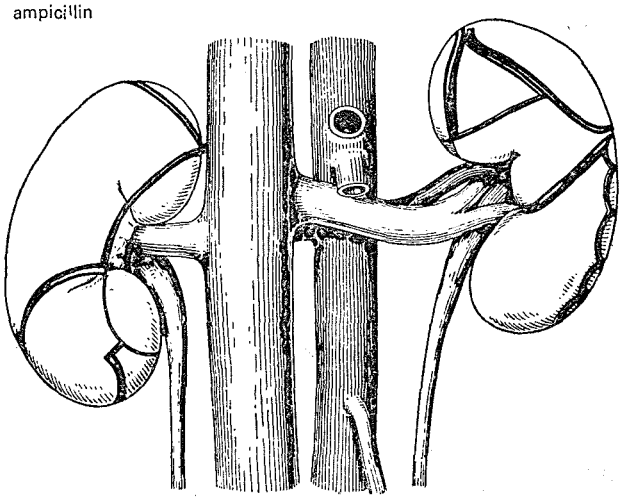

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