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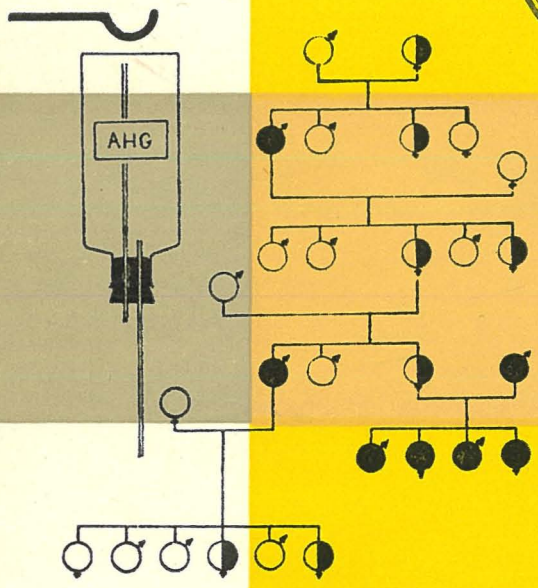

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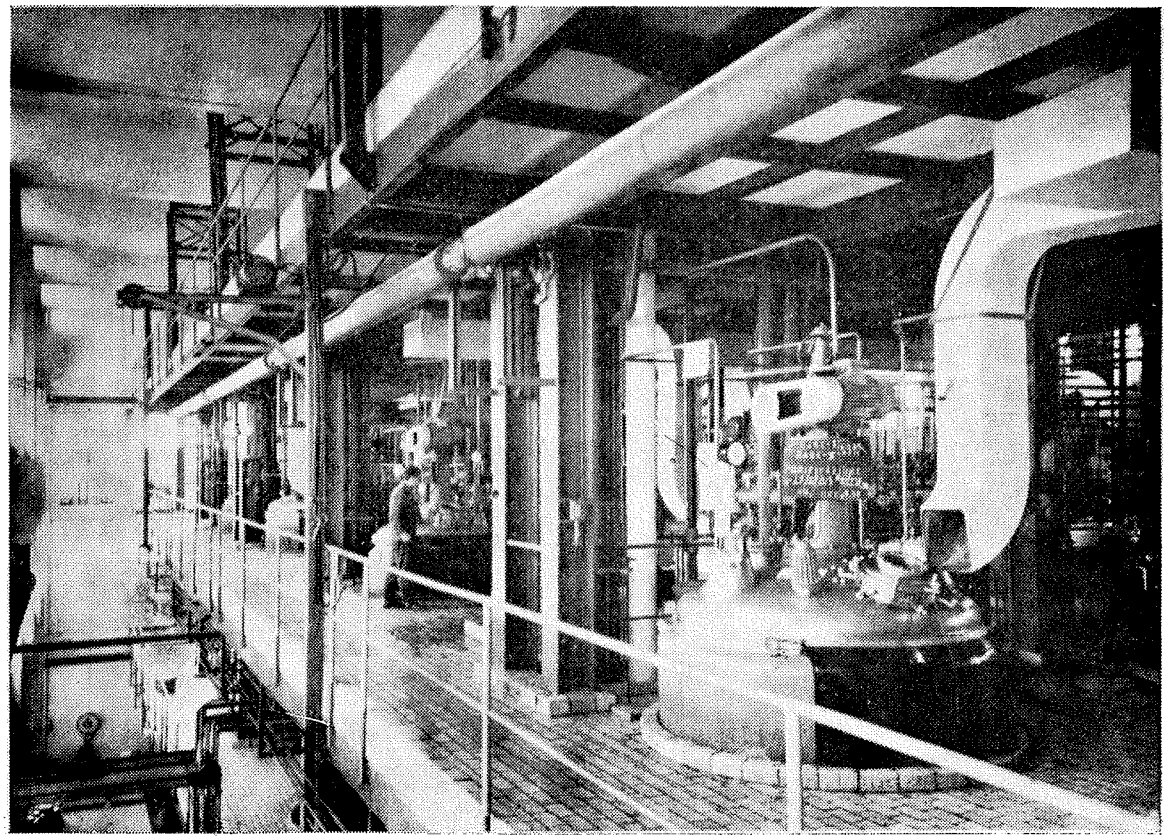

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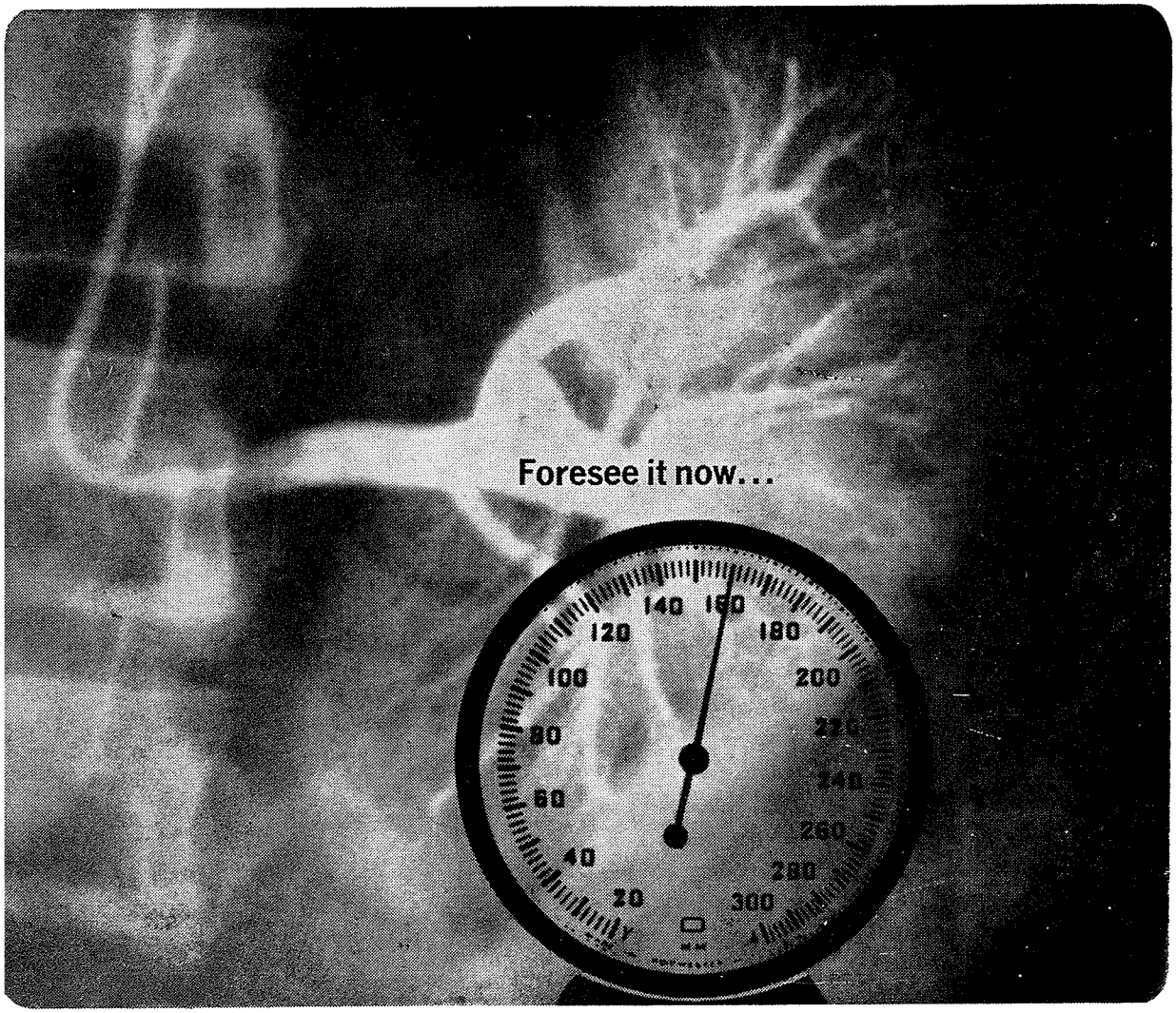

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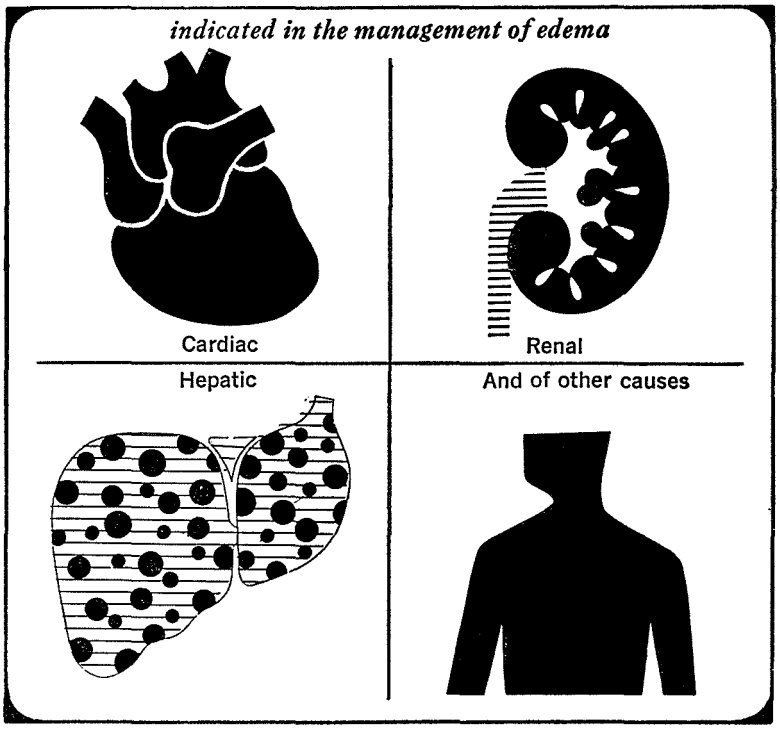

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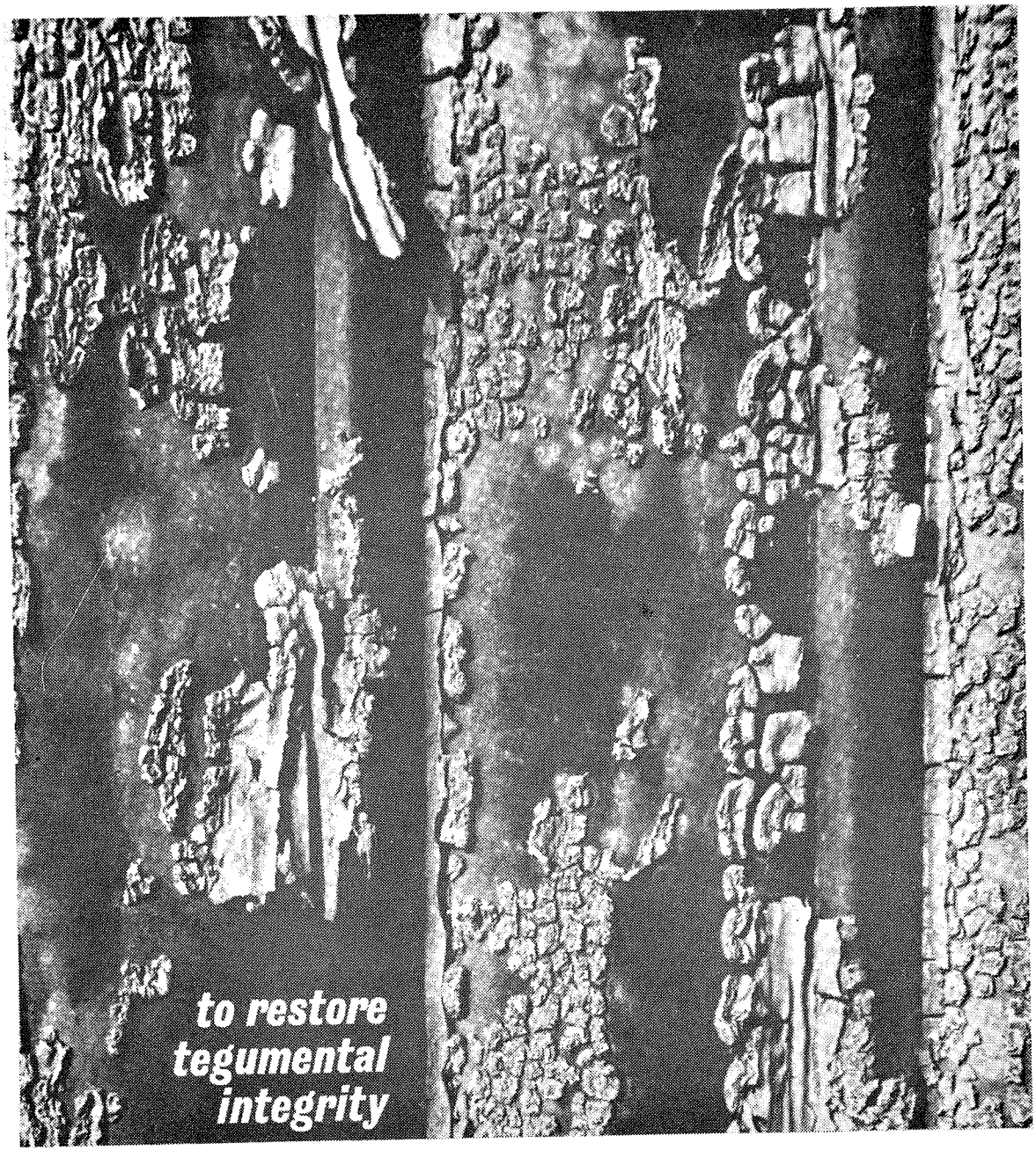

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EDITORIAL

There is a faction in our community who discourage criticism of our institutions, and, by comparison with others who are worse off, constantly try to remind us of how fortunate we are. This attitude is reactionary, leads to mediocrity and has no place in the modern world. It also leads to propagation of many "myths" which few take the trouble to check. One of them is our supposedly favourable student/teacher ratio. This is not substantiated if our figures are compared with those of medical schools in the U.K., which is, after all, more realistic than comparing them with Messina. In this issue we print a selective review of the recent report of the Royal Commission on Medical Education. This should dispel the other "myth" — that we are not in need of reform.*

It is lamentable that many people take the attitude that the "ideal" is an aim not to be taken too seriously as it can never be achieved. Some do not even bother to find out what constitutes the ideal. This must be condemned very vigorously as it is only in striving for the ideal that progress can be made. In fact, it was most encouraging to find this theme in the editorial of "Pmag", a newcomer to local student publications; more especially should one hope to see it being expressed by medical undergraduates, since the "relief of suffering" is not something one can do in the abstract.

So, let us be aware of our faults, as in doing so we show imagination, let us publicise our faults as this will earn us the respect and help of others. Above everything let us make an honest attempt at remedying these faults, as only this will gain us absolution. Let us also be modest about our past achievements and present virtues, and, rather than use them as a basis for complacency, let them be a springboard for greater achievements and more virtues in the future.

* World Directory of Medical Schools. — W.H.O. 1963

HAEMOPHILIA I:

DOES THE ANSWER LIE AT THE BOTTOM OF AN "ICEBERG"?

B. MACKENZIE CRONIN

In 1957 a total of 153 Haemophilic families in Great Britain was recorded (1). Comparing the population of Britain and Malta and assuming the same incidence ratio, one would expect to find only one family of Haemophiliacs in Malta, whereas, in fact, 18 affected families are known (2). Since the number of units comprising a family in Malta was higher than in Britain, then there is a relatively higher incidence in Malta than is suggested by the above comparison.

The greatest number of reported cases of Haemophilia occurs among the Germanic peoples of Northern Europe, Great Britain and North America. Fewer cases are reported among the Latin races, and in the Asiatic and Negro races it seems to be almost unknown (1).

WHY STUDY SUCH A RARE DISEASE?

In comparison with Arterial Diseases, Malignant Diseases, Rheumatoid and Osteo Arthritis etc. Haemophilia affects so few people that it almost seems superfluous to spend any time contemplating what is, after all, apparently a rare disease entity. It is more usual for the mechanism of Haemostasis to prove over-sensitive in the normal populace and a clot may form in some part of the intact circulatory system.

Thrombosis is all too commonly encountered by physicians and surgeons in the Western world. By the study of such rare conditions of lack of adequate Haemostasis new light might be thrown on the common condition of Thrombosis.

To enter the field of recent study of coagulation disorders is to be overwhelmed by the sheer volume of the material written, technical terminology used, and the controversial opinions held; but also it is to be enthralled by the ingenuity and perseverance shown by the great workers in this field.

HISTORICAL

WHAT IS HAEMOPHILIA?

This might be easier to answer by stating what it is not, but most standard textbooks of Medicine define Haemophilia thus:-

> "Haemophilia is a Hereditary Disease, affecting males but transmitted by females and characterised by a prolonged coagulation time and by lifelong tendency to excessive haemorrhage due to a quantitative deficiency of Anti Haemophilic Globulin".

The word Haemophilia is derived from the Greek, Haima meaning blood and philia meaning affection. The word was coined by Hopft in 1828.

The earliest documentation of what is assumed to be Haemophilia occurred in the 2nd Century A.D. in the Talmud. The Jews and the Arabs observed that occasionally after the traditional circumcision a young boy would bleed to his death. They recognised that this bleeding tended to recur in certain families and exempted such families from this rite. Does this represent one of man's earliest attempts at controlling Natural Selection?

The next significant step was the publication in 1820 of Nasse's Law or Rule which stated:

> "Women whose fathers were bleeders transmit the trait to their children even if married to normal men. In the women themselves and, in general, in no female person is the trait ever expressed".

1911 saw the publication of Bullock and Fildes' "Treasury of Human Inheritance" (3) which surveyed the whole of the relevant literature then available, the term Haemophilia being reserved to cover the condition in which the folowing criteria were to be observed:-

1. Liability to excessive bleeding which had existed from infancy and was restricted to the male sex.
2. Evidence of similarly affected males in the family and of transmission only by the apparently normal female.
3. Demonstration of prolonged clotting time and absence of any other abnormalities that may cause this bleeding.

These criteria established Haemophilia as a syndrome (a running together) of excessive Haemorrhage, occurring in males of certain families, whose blood demonstrated a greatly prolonged clotting time. These criteria at the same time eliminated the considerable amount of confusion which had existed in the latter part of the 19th Century concerning the term "Haemophilia", which had been used to cover such disease entities as Thrombocytopenic Purpura, Telangiectasia and others, even scurvy!

This classic concept of Haemophilia was held for over forty years. Research of the last twenty years indicated that this view had to be modified greatly. Haemophilia had always been

a multifaceted disease — presenting a different face to each observer, depending on the observer's viewpoint.

In 1943 the life expectancy of a Haemophiliac was no more than 16 years. Nowadays, with the advent of modern therapy, Haemophiliacs can look forward to reaching the age of 50 or 60. Men not undergoing treatment are even able to shave with a safety razor if they wish since if they cut themselves they bleed — but only for a normal length of time.

WHY DO HAEMOPHILIACS HAVE A NORMAL BLEEDING TIME?

Large injuries cease to bleed because of retraction of the blood vessels AND coagulation of the blood. Injuries perforating to a depth of less than 5 mm cease to bleed because capillary contraction reduces the size of the injured area which becomes covered with a mass of fused platelets which form thrombi.

For normal Haemostasis to occur in man three main groups of factors are required.

1. An adequate supply of NORMAL platelets.
2. Active contraction of capillaries in response to injury.
3. Coagulation of blood occurring in normal time.

The coagulation time of whole blood obtained by venipuncture in a Haemophiliac is usually greatly prolonged. (The venipuncture can be performed without danger because the elasticity of the vessel wall is sufficient to close the wound when the needle has been inserted into the vein at an angle).

From the above it thus *seems* likely that Haemophiliacs bleed unduly because of a defect in Blood Coagulation.

WHAT IS THE NATURE OF THE CLOTTING DEFECT IN HAEMOPHILIA?

The defect is believed to be due to a deficiency in Haemophilic blood of Anti Haemophilic Globulin (A.H.G. or Factor VIII) which is present in normal plasma.

When the presence of this factor was postulated there was no means by which its function in the normal coagulation process could be demonstrated. A curious method was devised for the diagnosis of Haemophilia:-

A sample of blood taken from an individual suspected of suffering from Haemophilia was added to a sample of blood of a known Haemophiliac. If the coagulation time of the known Haemophilic blood could not be shortened by the addition of the suspected blood then the suspected case was labelled a Haemophiliac.

The pathologist relied on an accurate Clinical Diagnosis being made in the first place!

In 1953 Biggs and Macfarlane found seven cases of *Supposed* Haemophilia in which there was *no* deficiency of AHG. but a deficiency of another factor previously unrecognised, and named it Christmas Factor (Factor IX). To add to the confusion this factor is also called Plasma Thromboplastin Component (P.T.C.).

Many "known" Haemophilic families including those of the Tenna Valley in Switzerland are now identified as suffering from deficiency of Christmas Factor. Also in 1953 Rosenthal observed in six supposed cases of haemophilia that there was neither deficiency of A.H.G. nor of Christmas Factor but deficiency of a factor labelled Plasma Thromboplastin Antecedent (P.T.A. or Factor XI).

WHAT WERE THESE NEW DEFICIENCY DISORDERS TO BE CALLED?

The classical view of Haemophilia could now be regarded as covering THREE disease entities all having the criteria, necessary to be fitted into Bullock and Fildes' interpretation of Haemophilia. Many new classifications were suggested to cover this new state of affairs. That they are three separate entities can be shown by the fact that A.H.G. added to a sample of blood lacking Christmas factor will not lower the clotting time of that sample, a sample of Haemophilic blood added to that of Christmas Disease reduces the clotting time. Biggs and Macfarlane use the terms Christmas Disease for the cases deficient in Factor IX and Rosenthal Syndrome for those deficient in P.T.A., reserving Haemophilia for those patients whose blood shows a deficiency of A.H.G. (1)

A further anomaly was added by the observation that some families existed suffering from a relatively mild form of Haemophilia in which the clotting time might be within normal limits but with grossly abnormal levels of A.H.G. (Merskey et al. 1949). Thus whilst a long clotting time probably indicates a severe defect, a short clotting time does not necessarily mean that the patient is mildly affected and has little diagnostic or prognostic significance.

AETIOLOGY

WHAT IS THE AETIOLOGY OF HAEMOPHILIA?

There seems little doubt now that although there may be other factors deficient, *the essential cause* of the Haemophilic clotting defect is A.H.G. deficiency, either apparent or real, since the clotting time of Haemophilic blood can be restored to normal by the addition of A.H.G. The observation by Tocantins et al in 1951 (4) that the coagulation of Haemophilic plasma can be made to approach that of normal plasma by nothing more complicated than appropriate and optimum dilution is intriguing.

On reflection, although the apparent anomaly of Haemophilic blood having a normal Bleeding Time can be explained on the basis of the vascular factor necessary for Haemostasis functioning normally, *why does a Haemophilic patient develop Haemarthroses so consistently?*

A Haemophiliac, if he can survive the rigours of teeth extraction and other traumatic experiences in childhood that could cause him to bleed to death, nevertheless may spend a considerable amount of his time in Hospital receiving medical and/or orthopaedic treatment for Haemarthroses and their consequences.

The tendency to such serious effusions and haemorrhages into joints, muscles and various organs in Haemophiliacs (in Great Britain there is a plea from several quarters to replace the three wheeler invalid cars supplied to Haemophiliacs with well sprung modern saloons in order to minimise minor traumata and so minimise the incidence of joint effusions and haemorrhages) all point to the existence of a *vascular abnormality* which is not fully explained by the defect in coagulation. Pavlovsky (1958) suggested that an undue fragility of the blood vessels was responsible.

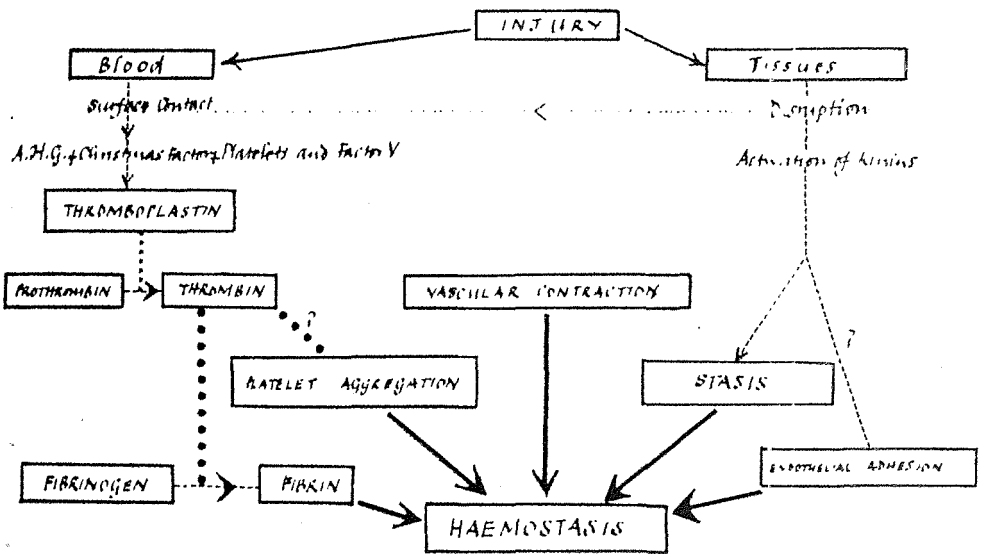
WHAT OF THE THIRD FACTOR NECESSARY FOR HAEMOSTASIS — THE PLATELETS?

Here again there had been an anomaly. When a sample of normal blood is withdrawn from a vein the platelets quickly disappear before clotting occurs. But in Haemophilic blood, under the same conditions, the platelets may be found in the still fluid blood hours afterwards. The phenomenon of viscid metamorphosis (first described by Wright and Minnon in 1917) or Platelet Aggregation had not occurred.

In 1956 Bergsagel showed that following contact with a foreign surface A.H.G., Christmas Factor and Ca++ react to form an "Intermediate Product" which then causes the aggregation of the platelets.

As a result of these changes a granular material is discharged from the platelets which, in the presence of Factor V is extremely active in converting Prothrombin. A deficiency of A.H.G. will prolong the time which is required for the initial changes to take place — thus prolonging clotting time. What may be more important is that it will reduce the amount of Thromboplastin formed and the amount of Prothrombin which is converted during the process of coagualtion. The end result of the coagulation process had been accepted to be Fibrin formation. (see Fig. 1)

FIGURE 1 : COAGULATION



WHY THEN IS AFIBRINOGENAEMIA LESS OF A DISABILITY THAN HAEMOPHILIA?

Afibrinogenaemia is a rare condition in which there is either Hereditary absence or an acquired absence of Fibrinogen. It presents a clinical picture resembling Haemophilia except that Haemarthrosis is very rare. Thrombin formation is normal and Platelet Aggregation occurs.

Thus it seems that Thrombin formation is more important to the Haemostatic mechanism as a whole than is Fibrin formation.

HOW CAN A DISEASE WHICH SYSTEMATICALLY ERADICATES ITS SUFFERERS BE CONSIDERED TO BE AN INHERITED DISEASE?

Haemophilia has been considered as a classical example of a sex-linked inherited disease. Perpetuation of the disease being considered to arise from the fact that a female may have one of her X chromosomes affected for Haemophilia but still be to all intents and purposes normal in phenotype. The mating of a Heterozygous (for Haemophilia) female with a normal Hemizygous (only one X) male producing sons in the ratio of one haemophilic to one normal and daughters in the ratio of one heterozygous to one normal. (see Fig. 2). In this way the apparently normal Heterozygous female can, it seems, transmit the disease in perpetuity, her one normal X chromosome being sufficient to prevent manifestation of her abnormal X. But selection against such an event is strong. Every time the gene is passed on to a male the chances of it surviving are considerably reduced.

When taking a Family History of Haemophiliacs it is necessary to enter into considerable detail.

Despite this, about a third of all cases in Britain will not show a Family History of the Disease apparently arising spontaneously. It was thought that these cases arose as a result of a mutation, the mutation occurring more frequently in males than in females (Haldane 1946). It was suggested that the genetic abnormality arose in the germ cell of the patient's maternal grandfather.

The pedigree of Haemophilia of the Royal Families of Europe strongly suggests that Queen Victoria was Heterozygous for Haemophilia. Since her father was normal, and there is nothing to suggest that her mother was a carrier, it seems likely that a mutation had occurred, most probably in her father's gametes. It is well known that the Romanoff family gene came to an abrupt end in 1817 and that the Spanish Royal Family branch of the Hapsburg family gene was extinguished as a result of car accidents. (see Haemophilia 3, Rizzo Naudi)

It has been calculated that the average life of a gene determining Haemophilia is little more than three generations (5). It is, of course, possible that the gene may sometime have been handed down through several generations of carrier females all of whom by a succession of fortuitous chances producing *only* normal sons, normal daughters and carrier daughters. This is highly unlikely. (see Haemophilia 2, Olivieri Munroe)

One could consider Haemophilia occurring in succeeding generations in the manner shown in Figure 3.

Thus it might be expressed that Haemophilia is a disease which occurs as a result of a mutation, may be transmitted to succeeding generations, and has a tendency to disappear from the line.

FIGURE 2

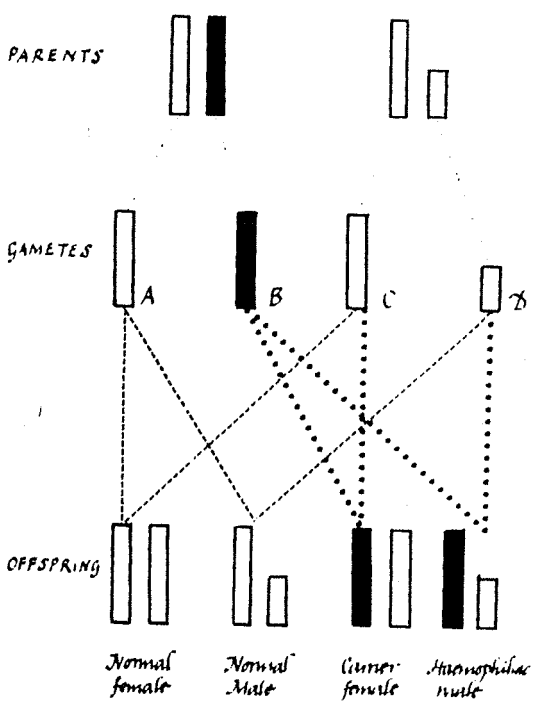
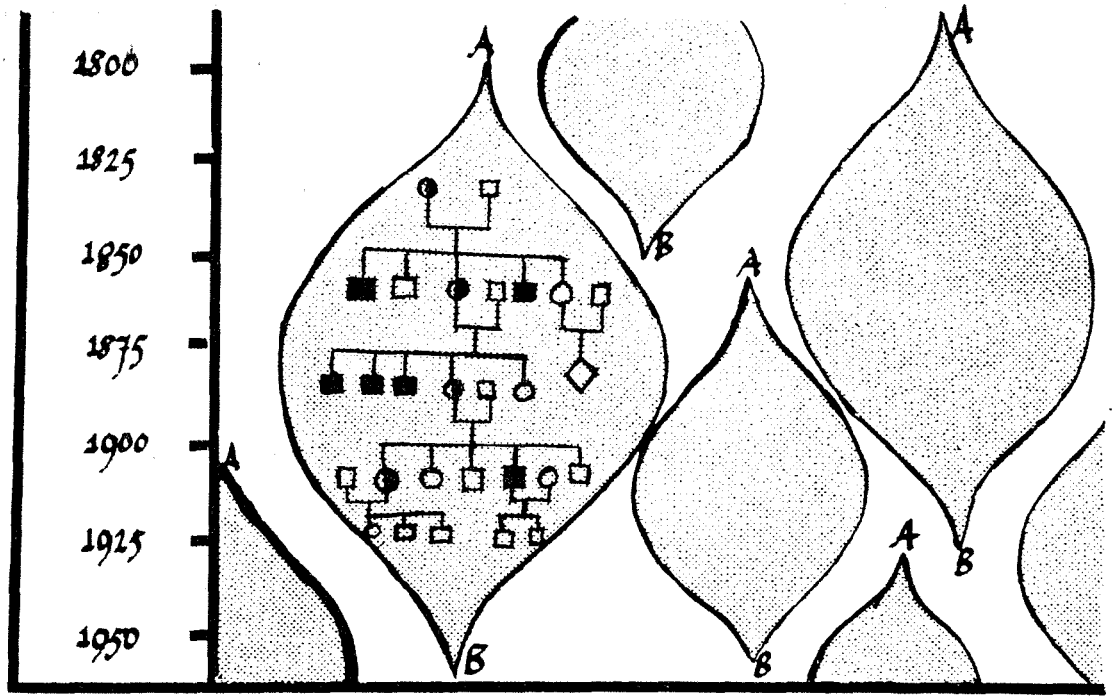


FIGURE 3



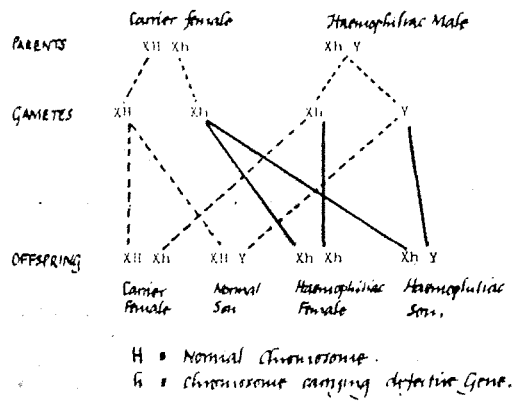
A - Mutation occurs initiating line

B - Natural or otherwise end of line

CAN ONLY MALES SUFFER FROM HAEMOPHILIA?

The union of a Heterozygous Female with a Male sufferer could theoretically arise:-

FIGURE 4



Graham and Brinkhouse succeeded in breeding Haemophilic dogs in this manner and produced the expected ratio of Haemophilic females. From figure 2 it may be postulated that a Haemophilic female could arise if gamete C had undergone a mutation. It was thought that females Homozygous for Haemophilia did not exist either because the combination Xh Xh (h being gene for Haemophilia) was a lethal combination to the zygote, or that they did exist (despite the chances against the above union being very high) but occurred so very rarely that they were unrecognised for what they were.

Cases of Haemophilia occurring in females have now been well documented, (1) which are almost certainly examples of such a union. It is calculated that only one female in 100,000,000 females can be expected to suffer from Haemophilia (5).

WHY IS IT THAT THESE FEMALE HAEMOPHILIACS BLEED NO MORE SEVERELY THAN MALE HAEMOPHILIACS?

Mary Lyon suggests that only one X Chromosome remains functional per cell of a diploid individual and that every female is a mosaic of two kinds of cells — those with the paternal X chromosome still acting and those with only the maternal X still acting.

In females one X only is acting the other X condenses to form the Barr body, in general present only in nuclei of female cells. This hypothesis could possibly explain the fact that a female haemophiliac (XhXh) will not suffer more severely than a male haemophiliac (Xh).

Might it be that, in a female heterozygous for haemophilia there could be a mechanism which relegates only the affected X chromosome to become the Barr body? This could account for the apparently normal phenotype of such a female. Or could it be that the mosaic effect is retained so that only half (say) of the Xh chromosomes are acting at any one time which would render a carrier female to show half the grade of severity of her hemizygous male counterpart? Macfarlane et al have shown that carrier females were more liable to excessive haemorrhage after tooth extraction than were the normal controls (6).

AETIOLOGY: A HYPOTHESIS:—

CAN HAEMOPHILIA BE ACQUIRED?

Another perplexing consideration can now be introduced. Various observations show that a disorder clinically indistinguishable from classical Haemophilia may be acquired during an individual's lifetime (7,8,9,10,16). Several cases have been well documented of such a condition arising following therapy with Penicillin. Other cases have been described following Horse Serum Therapy and after treatment with Sulphonamides. Specific Anticoagulants directed against A.H.G. were discovered to be present in those patients who were described as having a Haemophilia-like disease.

A well defined specific anticoagulant directed against the conversion of Prothrombin to Thrombin has been found with some frequency (10%) in patients with Lupus Erythematosus (16). Circulating anticoagulants directed against A.H.G. have been reported to occur spontaneously in otherwise normal individuals, and in as high as 21% with congenital Haemophilia (7).

Women in 3rd or 4th decades may suffer an onset of severe haemorrhage several weeks to years after parturition. From these observations Haemophilia could be represented as the main Theme and all these other conditions variously labelled as Pseudo-Haemophilia, Haemophilia-like diseases or Para Haemophilia as variations.

If one considers individuals who manifest a tendency to excessive haemorrhage and in whose blood can be demonstrated lack of A.H.G. (whether this is due to an absolute deficiency or not) then such cases may be classified as follows:-

HAEMOPHILIA or the
HAEMOPHILOID States:

I Congenital.

a) With family history of disease.
b) No family history. Possibly result of mutation.

II Acquired

1) As a result of a Drug Reaction (Penicillin, Sulphonamides, Horse Serum).
2) After Pregnancy — Iso-immunisation?
3) After administration of Porcine A.H.G.
4) Associated with Collagen Disease:
Systemic Lupus Eryhematosus,
Rheumatoid Arthritis,
Temporal Arteritis,
Regional Ileitis.

CONSIDERATIONS:

1. A Haemophilia-like state developing in a patient after Penicillin therapy might indicate an unfavourable reaction occurring twixt the Penicillin and the individual. In a recent article Green (8) showed that neither Penicillin nor its analogues are satisfactory antigens for A.H.G. inhibitors. Neither did the Penicillin form a coat on the A.H.G. molecule. A possible explanation could be that the disorder is the result of the altered allergic state that results from the Penicillin.

Normal Adult —— Penicillin Administration stimulates an Allergic Response ——}

Allergic State? established —} Haemophilia-like disorder. { a Clinical Hypersensitivity? }

Hypersensitivity could be said to be Auto Immune — but affected by an exterior source (18).

2. The appearance of circulating anticoagulants in cases of Systemic Lupus Erythematosus, Rheumatoid Arthritis, Temporal Arteritis and other so-called Collagen Diseases, might indi-

cate that the appearance of Pseudo-Haemophilia in these patients could fit in with Damashek's concept of the Hidden Iceberg (13). (see Fig. 5).

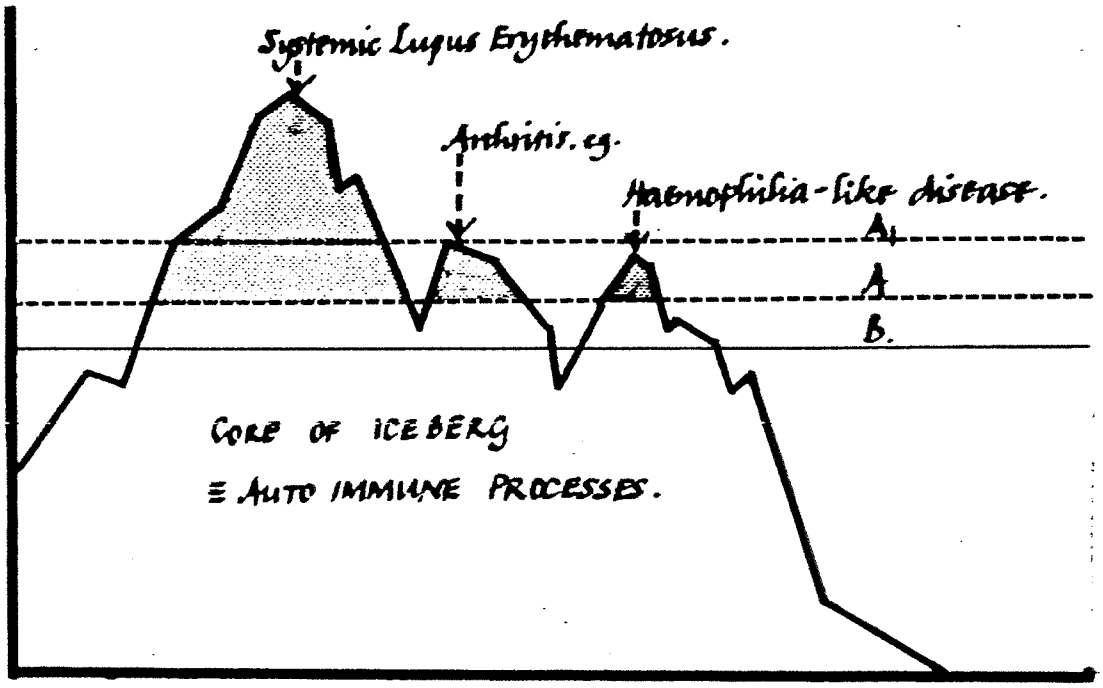
3. In those patients who develop a Haemophilia-like disease after treatment with Penicillin, therapy with *Prednisone* brought about a remission (7). Abilgaard et al in 1965 noted the cessation of Haematuria in 3 Haemophiliacs after 6 to 48 hours therapy with Intravenous Hydrocortisone (50 mg every 8 hours) or oral Prednisone (20-25mg every 6 hours for 1 to 4 days). (11)

4. Kasper et al in 1964 observed that in 5 pregnant known carriers of Haemophilia with low A.H.G. levels *there was a significant rise in A.H.G.* which averaged twice the non pregnant levels. This increase was not reflected in cord blood. One of the pregnancies resulted in a severely haemophilic newborn — both cord and baby's blood were practically devoid of A.H.G. (12)

5. Most of the anticoagulants developing in patients with classical Haemophilia have been shown to inhibit Factor VIII specifically in a reaction dependent both on time and tempera-

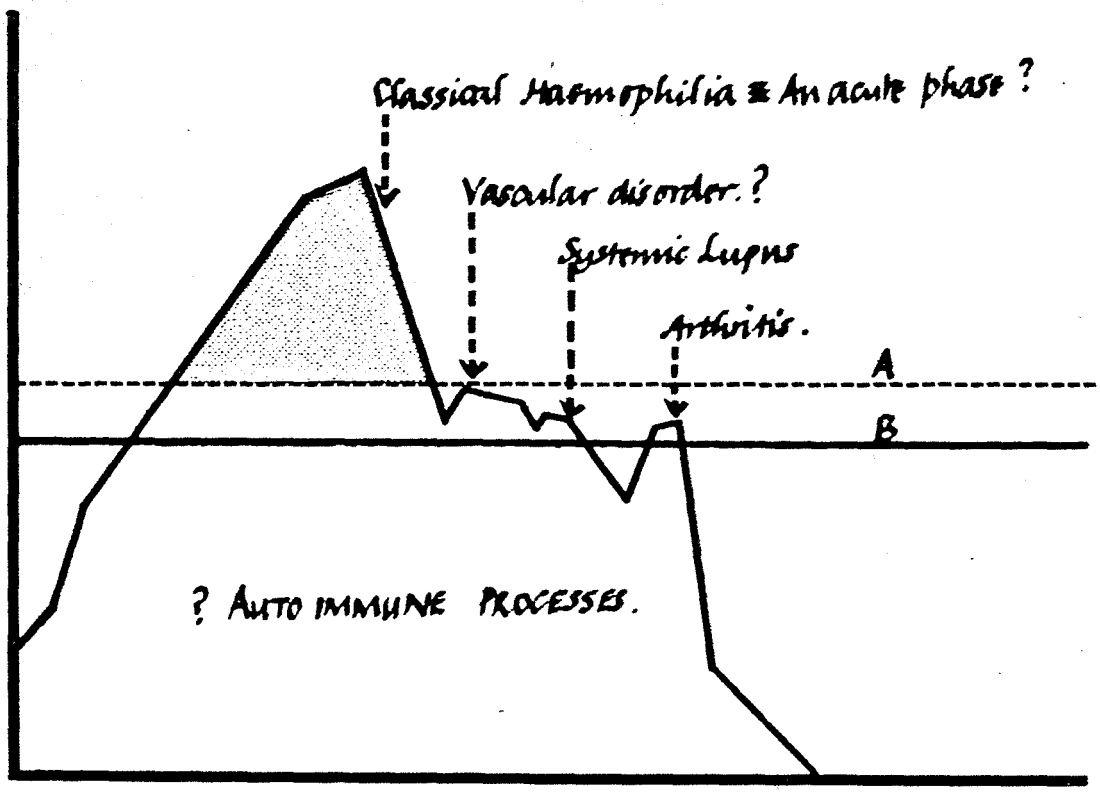
Often, more than one type of Auto Immune lesion may occur in the same individual.

FIGURE 5



A_1 – Level at which Clinical recognition was possible in 1940.
A - Level at which Clinical recognition is now possible.
B - Normality Level.

FIGURE 6.



ture suggesting to some workers that the inhibitor was an enzyme. Other workers believed these circulating anticoagulants to be antibodies since they could be recovered from the gamma globulin fraction after electrophoresis of serum or plasma. Green showed that the A.G.H. inhibitors of both Spontaneous and Haemophilic origin were IgG globulins. (9)

In view of the above points it is tempting to think of adding "Haemophilia" to the growing list of Diseases which are labelled Auto-Immune. (see Fig. 6).

Could it be that the mutant Gene or one of its intermediate or end products is not recognised as being "Self"? William Damashek in his Introduction to a Symposium (published 'Blood' in 1954) wrote:-

> "Until recently Haemophilia was easily defined and readily recognised. However, in the last few years various active workers in the field have unearthed new facts, developed new hypotheses and have had the temerity to claim that Haemophilia may not be actually what it seems".

CONCLUSION

The Question — *"Why is there an apparently higher Incidence of Haemophilia in Malta?"* — has now developed a greater significance. In genetic terms Malta appears to be an ideal population isolate. The Hardy-Weinberg equation can not be applied to the case of Haemophilia since the possession of the affected gene reduces fertility and will progressively be eliminated from the population (excluding mutational possibilities). Also there are unlikely to be random matings — since haemophilic males tend not to marry (as the result of genetic counselling), and the female sibs of known Haemophiliacs are warned that they ought not to have children.

If one considers any single individual Maltese now living — say Mr. X, then Mr. X would have 2 parents, 4 grandparents, and 8 great grandparents etc. Assuming that in any one century there occur four generations and if there was no consanguinity amongst Mr. X's ancestors, then the number of ancestors would be 2 to the power of n where n represents the number of ancestral steps removed from the

individual. (17) Over a period of 400 years then 2^n would be 2 to the power of 16 = 65,136. Thus the population of Malta in 1560 should have been at least 65,000 for there *not* to have been consanguineous marriages. In 1530 a preliminary report made for the Knights of Malta assessed the population of the Island at 12,000 inhabitants. (14) (According to this calculation the population of the World should have been one million million ancestors for there to have been no consanguinity. The estimated population of the world 300 years ago was only 500 million at the most. The Brotherhood of Mankind is a genetic reality!). Although consanguinity will affect the recessive alleles and tend to expose recessive traits, where a lethal gene is concerned a high rate of consanguinity will tend to remove it at a faster rate than in a population isolate where the rate of consanguinity is less.

Can the higher incidence of Haemophilia in Malta be linked with the high incidence of Diabetes Mellitus? (15) What is the relative incidence of other known Auto-Immune diseases in Malta, and could there be present some factor to a greater degree in Malta than elsewhere?

A higher mutation rate is unlikely — despite Malta's incomparable climate — since Haemophilia appears to be rarer in surrounding countries.

Nossal has described Medicine as having entered The Golden Age of Immunology. Immunologists made Cardiac Transplantation a reality — the "Iceberg" may soon have its depths revealed.

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HAEMOPHILIA 2:

SOME MANIFESTATIONS OF HAEMOPHILIA

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Present day concepts on haemophilia have altered since Bullock and Fildes (1911) established the disease as clinical entity Since then Christmas disease (Biggs et al, 1952) was separated from classical haemophilia, and other distinct conditions such as P.T.A. (Plasma thromboplastin antecedent) by Rosenthal et al (1953). Originally haemophilia was restricted to excessive bleeding disorders manifested from infancy, restricted to the male sex and transmitted by apparently normal females. Now, evidence of similar conditions arising in adult patients is forthcoming and apparently, 25-30% of all cases appear to have no family history of the condition. (Biggs and Macfarlane, 1957). The nomenclature of congenital deficiencies of blood coagulation factors and mode of inheritance is shown in Table 1. This paper is restricted to a consideration of some manifestations of classical haemophilia, (Haemophilia A, Biggs and Macfarlane, 1957) and illustrated by means of three family histories, two Maltese and one an Italian family resident in Malta.

EARLY LIFE AND CHILDHOOD

The inherited type of haemophilia is almost invariably manifested in early childhood and then persists for life. Umbilical cord bleeding appears to be rare but severe haemorrhage following circumcision is more common. During the first year of life the child is to some extent protected in his environment of bed or cot. Some episode is frequent in this period even if only a tendency to bruise easily. Craw-

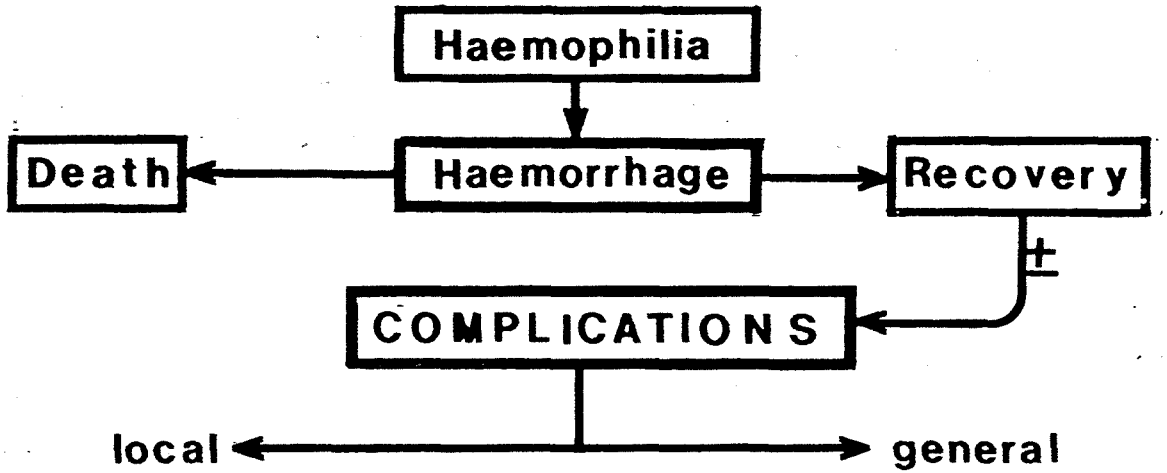
ling or walking multiplies the chances of trauma against hard or sharp objects or by falls. Commonly this type of injury affects the face resulting in epistaxis, or bleeding from a lacerated tongue, frenulum or gum. This bleeding may be profuse and necessitate blood transfusion, or even be the cause of death. In fact, no source of haemorrhage, no matter how trivial, may be regarded of little import in an haemophiliac.

The eruption of the deciduous teeth and their subsequent exfoliation present a further hazard to the growing child. Until recently the chances of trauma or haemorrhage of dental origin were responsible for the death of a large number of haemophiliacs during the first few years of life. As will be seen, today the picture has changed considerably.

Bleeding may be spontaneous or secondary to trauma or infection. It may be external, affecting skin, nose, mouth, gastro-intestinal or renal tracts, or it may be internal into a body cavity or tissues. The amount of blood lost into the tissues may be very large. The consequences of this haemorrhage are shown in Fig. 1 Severe bleeding, if uncontrolled will result in death. If mild, or if controlled energetically the patient may survive, usually to face recurrent bouts of haemorrhage from time to time. It is the complications of these repeated episodes that the haemophiliac has to face today. This is the price of survival.

TABLE I

FACTOR		CONGENITAL DEFICIENCY		
Inter. Nomen.	**Some Synonyms**	**Name**	**Synonyms**	**Inheritance**
I	Fibrinogen	Afibrinogenaemia		Autosomal Recessive
II	Prothrombin	Prothrombin deficiency	Hypoprothrombinaemia	"
V	Proaccelerin, labile factor	Factor-V deficiency	Parahaemophilia	"
VII	Proconvertin, stable factor	Factor-VII Deficiency	Hypoproconvertinaemia	"
VIII	Antihaemophilic factor (AHF) Antihaemophilic factor A. Antihaemophilic globulin (AHG)	Haemophilia	Haemophilia A	Sex-Linked Recessive
IX	Christmas factor, plasma thromboplastin component (PTC), antihaemophilic factor B	Christmas disease	PTC deficiency, Haemophilia B, deuterohaemophilia	"
X	Stuart-Prower factor.	Factor-X deficiency	Stuart defect, Prower defect.	Autosomal Recessive
XI	Plasma thromboplastin antecedent (PTA), antihaemophilic factor C	Factor-XI deficiency	PTA deficiency haemophilia C, Rosenthal's syndrone	"
XII	Hageman factor	Hageman trait		Autosomal Recessive
XIII	Fibrin stabilizing factor (FSF)	Factor-XIII deficiency	FSF deficiency	"



Haemarthrosis → impaired function / crippling deformities

Obstruction → necrosis, atrophy - limbs / abd organs

Haem. → mouth / neck → asphyxia

Haem → brain → CNS disturbances

Social problems → male → private life / work

Social problems → female → children – ?

FIG 1.

HAEMARTHROSIS

Of the many complications, haemarthrosis is one of the most common. Haemorrhage into the joints is usually accompanied by great pain and swelling. The commonest joints affected are the ankles, the knees and elbows. The shoulders, wrists and hips are also affected but to a lesser extent. (Smith, 1966). In acute haemarthrosis there is severe pain, swelling, heat, tenderness and limitation of movement. The early haemorrhages are resorbed, however recurrence usually causes extensive damage. There is thickening of synovial membranes, destruction of articular surfaces and bone. Repeated attempts at repair lead to fibrous tissue formation. Contractures then cause permanent crippling and/or limitation of function. This picture is so common that it has been used as a grading method for the severity of the disorder. Frequent or severe haemarthrosis indicate a severe haemophilia with usually completely absent Factor VIII. Less frequent or less severe joint involvement indicate the moderate case while the patient with only rare haemarthrosis is a mild one.

REORGANISATION OF HAEMATOMAS

As in the case of joints, the reorganization of haematomas in other areas can result in further abnormalities. Such a process occurring in or around a nerve bundle can lead to paralysis of the area supplied. Such a nerve may also be outside the site of haemorrhage but still be involved in subsequent contractures. In the brain spontaneous haemorrhages damage directly and their effect is dependent on the site of injury.

PRESSURE EFFECTS

Haemorrhage into the tissues or body spaces can result in manifestations due to pressure effects. Thus the arterial supply to a limb or organ may be impeded by such pressure effects. Necrosis or atrophy of the limb or organ could follow. In the region of the neck, haemorrhage into the lax tissue spaces can embarrass the respiration sufficiently to cause asphyxia.

In some cases the haemorrhage may present problems of differential diagnosis. An example is haemorrhage into the retroperitoneal space, or mesentery. The symptoms may simulate an acute abdominal emergency such as an appendicitis or perforating ulcer. A mild leucocytosis may add to the diagnostic difficulties.

Haematuria is common and usually persistent in spite of treatment. It may be spontaneous or follow trauma, eg., a fall or motor vehicle accident.

CASE HISTORY I

The patients belonging to the Maltese family shown in Fig. 2 are proved haemophiliacs with a Factor VIII level of 0%. The nine patients to be described have all been traced to one common source, their grandfather, A.M., who was a known bleeder and who died at the age of 58 years from a severe epistaxis. The family is a good example of the mode of inheritance of a sex-linked recessive gene and shows how it can skip a generation because all the male children of a generation are normal, while all the female children are carriers of the gene but are clinically normal. The family also illustrates the better prognosis for haemophilia today. All ten children in generation 2 died soon after birth, while of generation 4, all except two are alive and the deaths were a consequence of a severe fall in one case and a car accident in the other.

The family illustrates well the classic ways of presentation of haemophilia. The first three children of these families only came to the attention of a medical practitioner after the age of one year when they started walking and so had the chance of falling on their faces. All three suffered laceration of their upper labial frenulum which bled profusely. Later children were observed more closely and were noticed to bruise easily in the cot or pram.

The following patients are 4th generation members of the family shown in Fig. 2:

Patient no. 1.

First child. Died at age of 6 years following an intra-cranial haemorrhage after a car accident. He presented at the age of $1\frac{1}{2}$ years because of a cut upper labial frenulum. Required admission.

Patient no. 2.

14 years old, alive.

First episode prior to 12 months old — joint swelling from trauma in pram. Also cut upper labial frenulum with prolonged bleeding. Repeated admission to St. Luke's Hospital for bleeding episodes.

Patient no. 3.

12 years, alive.

Parents became more attentive and noticed that the child bruised very easily at about the age of 6 months when he became more active. At 2 years episodes of marked epistaxis.

Patient no. 4.

9 years old, alive.

At 7 months noticed tendency to bruise easily when exerting himself in bed. At the age of $1\frac{1}{2}$ years fell from table and has since been suffering from paraplegia.

Patient no. 5.

14 years old, alive.

First episode at 10 months when he cut his upper labial frenulum following a fall.

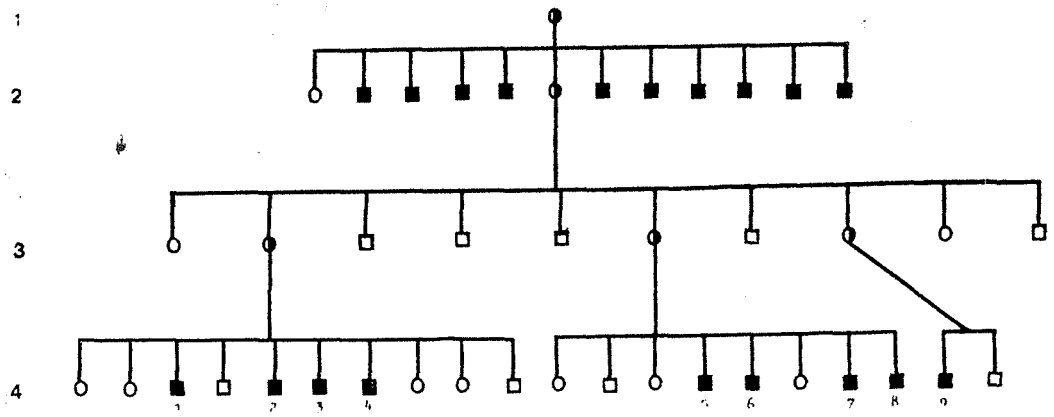


FIG. 2 Maltese family

Patient no. 6.
Died at 10 years after a severe fall.
St. Luke's Hospital. Internal haemorrhage, ruptured spleen, haematuria.

Patient no. 7.
7 years old, alive.
First episode = joint swellings following minor trauma.

Patient no. 8.
$4\frac{1}{2}$ years old, alive.
First episode = joint swellings following minor trauma.

Patient no. 9.
6 years old, alive.
First episode = joint swelling following falls in cot.

DENTISTRY IN HAEMOPHILIA

Apart from the above manifestations of this disease, iatrogenic causes add to the list. Major surgical procedures have no place in this paper, however minor oral surgery is almost inevitable in the life of the ordinary person and unfortunately the haemophiliac is no exception. The patient or his parents have a natural dread of the dentist. Neglect of the mouth makes future extractions inevitable with resulting grave problems in oral surgery. The importance of dentistry in haemophilia commences in early life with eruption of the deciduous dentition, as the following case history testifies:

CASE HISTORY II

Patient: Male, 23 years

Haemophiliac. First episode of bleeding occurred at the age of seven years. The boy noticed a loose temporary tooth during school. He played with it with his tongue and it was loosened completely. Bleeding followed at a slow but steady oozing. In order not to attract attention he swallowed the blood until time came to go home. He fainted three times on the way home and only reached there with assistance. At home the situation called for blood transfusion. Today, after a lifetime of hospital admissions for haemarthrosis and other complications the patient has a neglected mouth that necessitates extensive dental extractions.

CASE HISTORY III

The permanent dentition has an even worse record in haemophilia. The Italian family described in Figure 3 illustrates this well. In generation 3, the five members who manifested haemophilia have all died, two of them as a result of dental intervention.

Member no. 1. Died at 4 years; fell, internal haemorrhage.

Member no. 2. Died at 6 months; melaena and haematemesis.

Member no. 3. Died at 14 years; *tooth extraction*

Member no. 4. Died at 1 month; Haematemesis.

Member no. 5. Died at 28 years; *tooth extraction.*

Since going to print, one of the 4th generation males, aged 13 months until now presumed free of the condition and shown as such in the Figure 3, has shown severe bleeding tendencies. Following a fall, he cut a frenulum. This necessitated admission to hospital and blood transfusion.

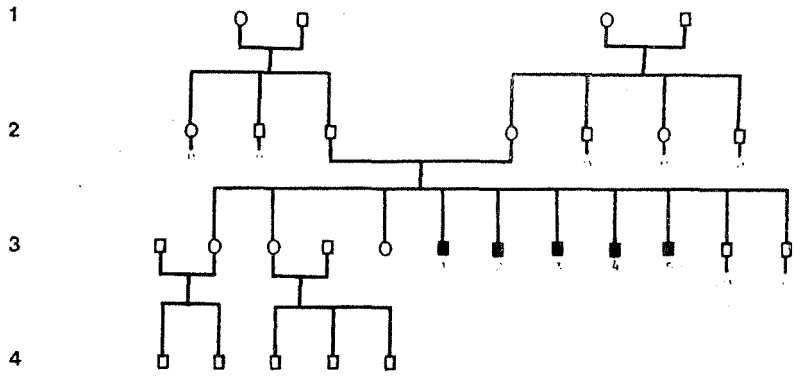


Fig. 3. ITALIAN FAMILY n=apparently normal

Local regional anaesthesia may also be accompanied by disastrous consequences. Block injection of the inferior dental nerve has been followed by death on occasion due to intractable haemorrhage into the soft tissues around the pharynx and in the neck. (Archer and Zubrow, 1964; Parnell, 1964). One of the authors has experience of blood transfusion being necessary following a prick in the ear of a haemophiliac for a blood count.

SOCIAL FACTORS

Secondary manifestations of haemophilia may take the form of social problems. The consequences of a life with possible disaster round the corner and frequent in-patient episodes cannot be without some mental trauma. The "carrier" girl who is otherwise normal also may face grave problems made worse since she cannot know beforehand whether her future children will be haemophiliacs or not. In these Islands these personal problems are augmented by the social stigma which the disease carries. Frequent hospitalization makes employment difficult and it is easy to develop feelings of inferiority and depression under these circumstances. A case such as this occurred recently at St. Luke's Hospital. The attempted suicide was treated successfully but the problem remains.

An attempt has been made to discuss some aspects of the manifestations of haemophilia, direct, indirect, social or psychological. Today rapid advances in therapy may soon eliminate the drip and blood transfusion. Concentrated preparations of Factor VIII may lead to outpatient treatment for all but a few cases of haemorrhage. This would mean less absenteeism from work and a greater feeling of self reliance. However much remains to be done in the way of education of the people to accept these patients as useful members of society. Dental education is also required to emphasise the need for continuous prophylactic and preventive measures in order to avoid the dangers of oral surgical procedures.

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le cose più grandi di lui...

DINISTENILE

fiale
supposte

DINISTENILE-B_{12}

fiale (*)
enterole

ricostituente
neuroenergetico
antipsicastenico
antistress

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DINISTENILE

psychosomatic energetic, antipsychasthenic, antidepressive agent

indications

States of physical and psychic exhaustion; endogenous depressions; neuropsychasthenia; psychosomatic diseases; depression; personality insufficiency (timidity, apathy, lack of self-confidence); convalescence, asthenia.

packs

ampoules

box of 6 ampoules of 2 ml

DINISTENILE B12

indications

All indications of Dinistenile, **especially in cases where,** in addition to strengthening the effects proper to Dinistenile, **a general eutrophic action is desired.**

characteristics:

This drug is an association of a corticoid hormone endowed with psychoenergetic activity, and of succinonitrile which exerts a neurotrophic activity. The synergism of action between these two drugs improves the psychic and physical capacity of exhausted and asthenic patients, and invigorates the affective sphere of depressed patients. Dinistenile is very well tolerated, as the hormone contained in the drug does not give rise to any other effects except those related to its activity as a tonic and normalizing agent on the psychic and physical sphere. Moreover, Dinistenile is readily absorbed by intramuscular and rectal route and guarantees a prompt and complete therapeutic effect.

HAEMOPHILIA 3:

HAEMOPHILIA AND EUROPEAN HISTORY

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Haemophilia must be one of the most important diseases that have affected the Royal families of Europe and the well documented pedigree for haemophilia of the family line of Queen Victoria, shown in Fig. 1, is certainly one of the most interesting for students of history and medicine.

Queen Victoria had one haemophiliac son, Leopold, Duke of Albany No. 8, II Generation, and two daughters, Alice and Beatrice, who were carriers of the sex linked gene for haemophilia. These two daughters transmitted the disease to the Royal families of Russia, Spain and Prussia.

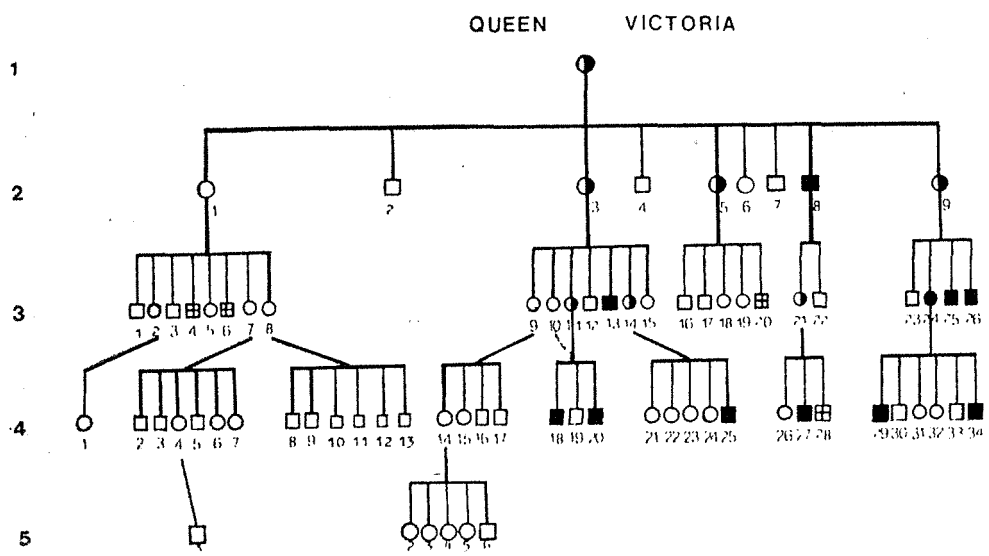
The first of these daughters, Alice, married Prince Louis of Hesse by whom she had one haemophiliac son and two daughter carriers. One of these daughters, Alexandra No. 14, III Generation, married Nicholas II, Czar of Russia. The Czarevitch, who was affected with haemophilia, came after four daughters. The knowledge that he was affected with this bleeding disorder must have been a great shock to his mother, who fell under the influence of quacks and soothsayers, the most notorious being the monk Rasputin, who by claiming to work remarkable cures, acquired great influence at court, alienated millions of Russians from the monarchy and so helped prepare the way for the revolution.

Beatrice, No. 9, II Generation, the other daughter carrier, married Prince Henry of Battenberg, by whom she had two haemophiliac sons and one daughter carrier, Victoria Eugenie, No. 24, III Generation, who married King Alfonso XIII of Spain. Two of their sons, Alfonso the heir (No. 29, IV Generation) and Gonzalo (No. 34, IV Generation), were affected with the disorder.

Although neither the dethronement of the Czar, nor of Alfonso XIII of Spain was the direct result of the fact that their heirs were haemophiliac, there can be little doubt that the knowledge that the successors to the throne were invalids, played an important part in the fall of these two monarchies.

Haemophilia was also transmitted to the Royal Family of Prussia through Irene, No. 2, III Generation, sister of the Czarina, who married her cousin, Prince Henry of Prussia.

It is interesting to note that another sister of the Czarina, Victoria, No. 9, III Generation, was the grandmother of Prince Philip, Duke of Edinburgh; luckily she was not a carrier of the gene and so did not transmit the disease to her offspring.



I

1. Victoria, 1819-1901, Queen of England.

II

1. Victoria, 1840-1901 X Frederick III, Emperor of Germany.
2. Edward VII, 1841-1910, King of England.
3. Alice, 1843-1878, X Prince Louis of Hesse.
4. Alfred, 1844-1900, Duke of Edinburgh.
5. Helena, 1846-1923, X Prince Christian of Schleswig-Holstein.
6. Louise, 1848-1939, X Duke of Argyll.
7. Arthur, 1850-1942, Duke of Cannaught.
8. Leopold, 1853-1884, X Princess Helena of Waldeck.
9. Beatrice, 1857-1944, X Prince Henry of Battenberg.

III

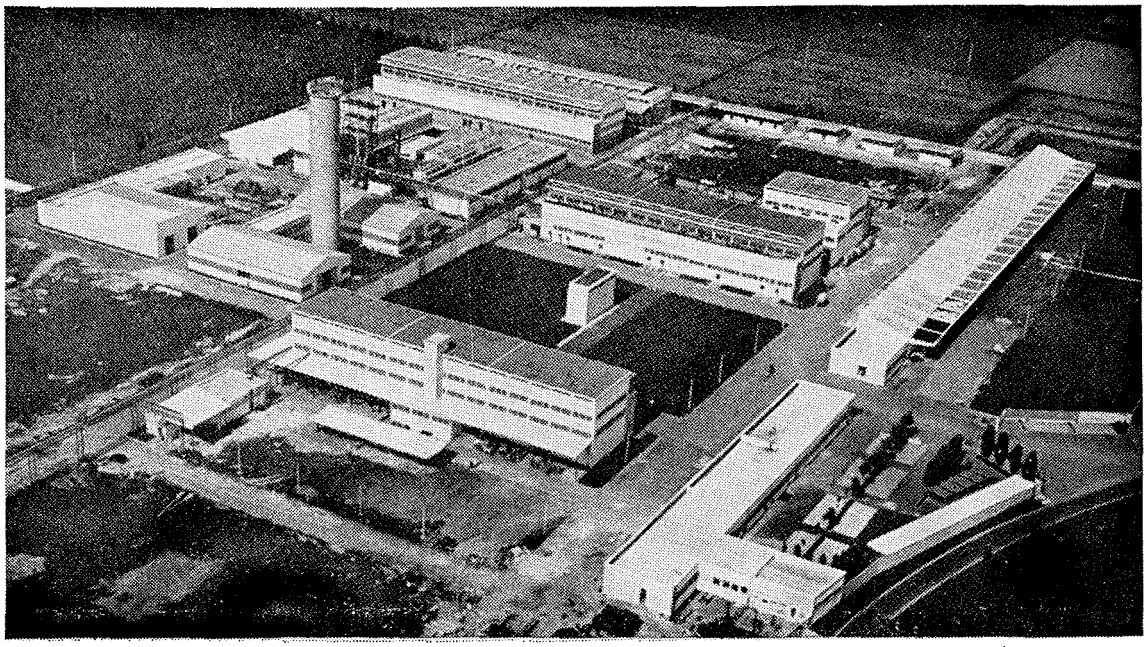
1. William II, 1859-1941, Emperor of Germany.
2. Charlotte, 1860-1919, X Duke of Saxe-Meiningen.
3. Henry, 1862-1929, Prince of Prussia.
4. Sigismund, 1864-1866.
5. Frederica, 1866-1929.
6. Waldemar, 1869-1879.
7. Sophie, 1870-1932, X Constantine, King of Greece.
8. Margaret, 1872-1954, X Frederick, Duke of Hesse-Cassel.
9. Victoria, 1863-1950, X Prince Louis of Battenberg (Marquess of Milford Haven).
10. Elizabeth, 1864-1918, X Grand Duke Sergius of Russia.
11. Irene, 1866-1953, X Prince Henry of Prussia (see III(3)).
12. Ernest, 1868-1937, Grand Duke of Hesse.
13. Frederick William, 1870-1873.
14. Alexandra, 1872-1918, X Nicholas II, Czar of Russia.
15. Mary Victoria, 1874-1878.
16. Christian Victor, 1867-1900.
17. Albert, 1869-1931.
18. Victoria, 1870-1948.
19. Marie Louise, 1872-1956.
20. Harold, 1876-1876.
21. Alice, 1883... , X Earl of Athlone.
22. Charles Edward, 1884-1954 Duke of Albany.
23. Alexander, 1886— , Marquess of Carisbrooke.
24. Victoria Eugenie, 1887— , X Alfonso XIII of Spain.
25. Leopold, 1889-1922, Lord Mountbatten.
26. Maurice, 1891-1914, Prince of Battenberg.

IV

1. Feodora Maria, 1879-1898, X Henry XXX of Reuss.
2. George II, 1890-1947, King of Greece.
3. Alexander, 1893-1920, King of Greece.
4. Helena, 1896— , X Carol II of Romania.
5. Paul, 1901— , King of Greece.
6. Erene, 1904— .
7. Catherine, 1913— .
8. Frederick William, 1893-1916, Prince of Hesse.
9. Maximilian, 1894-1914.
10. Philip, 1896— .
11. Wolfgang, 1896— .
12. Richard, 1901— .
13. Christoph, 1901— .
14. Alice, 1885— , X Prince Andrew of Greece.
15. Louisa, 1889— , X King Gustav VI Adolf of Sweden.
16. George, 1892-1938, Marquees of Milford Haven.
17. Louis, Lord Mountbatten, 1900— .
18. Waldemar, 1889-1845, Prince of Prussia.
19. Sigismund, 1896-1827.
20. Henry, 1900-1904.
21. Olga, 1895-1918, Grand Duchess.
22. Tatiana, 1897-1918, Grand Duchess.
23. Maria, 1899-1918, Grand Duchess.
24. Anastasia, 1901-1918, Grand Duchess.
25. Alexis, 1904-1918, Czarevitch.
26. May, 1906— , X Sir Henry Abel-Smith.
27. Rupert, 1907-1928.
28. Marie, 1899-1918, Grand Duchess.
29. Alfonso, 1907-1939, Prince of Asturias, later Count of Covadonga.
30. Jaime, 1908— .
31. Beatrice, 1909— .
32. Maria, 1911— .
33. Juan, 1913— .
34. Gonzalo, 1914-1934.

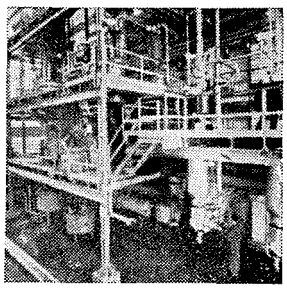
V

1. Michael, 1921— , King of Romania.
2. Margarita, 1905— , X Godfrey of Hohenlohe-Langenburg.
3. Theodora, 1906— , X Margrave of Baden.
4. Cecilie, 1911-1937, X Grand Duke of Hesse.
5. Sophie, 1914— , X Christopher of Hesse.
6. Philip, 1921— , Duke of Edinburgh.



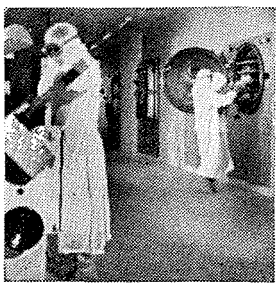
THE NEW, LARGE CARLO ERBA PLANT AT RODANO (MILAN).

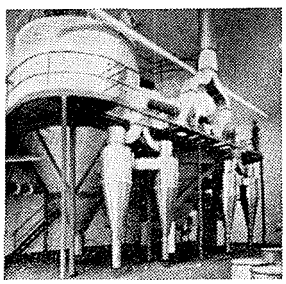
IN THE VANGUARD OF RESEARCH AND PRODUCTION



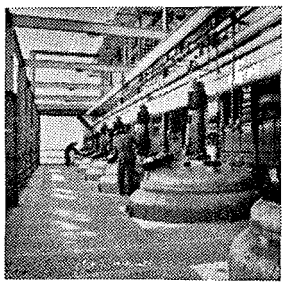
DETAIL OF THE CHLORAMPHENICOL PLANT (MILAN)

LYOPHILIZATION PLANT (MILAN)





DETAIL OF THE PLANT FOR THE PRODUCTION OF MONTEFIORE POWDERED MILK (OZZANO TARO).



DETAIL OF THE NICOTINIC ACID PLANT (RODANO)

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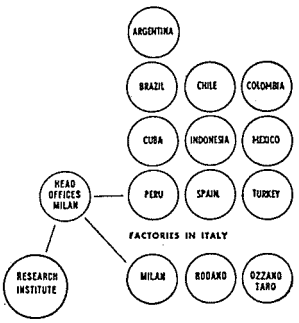

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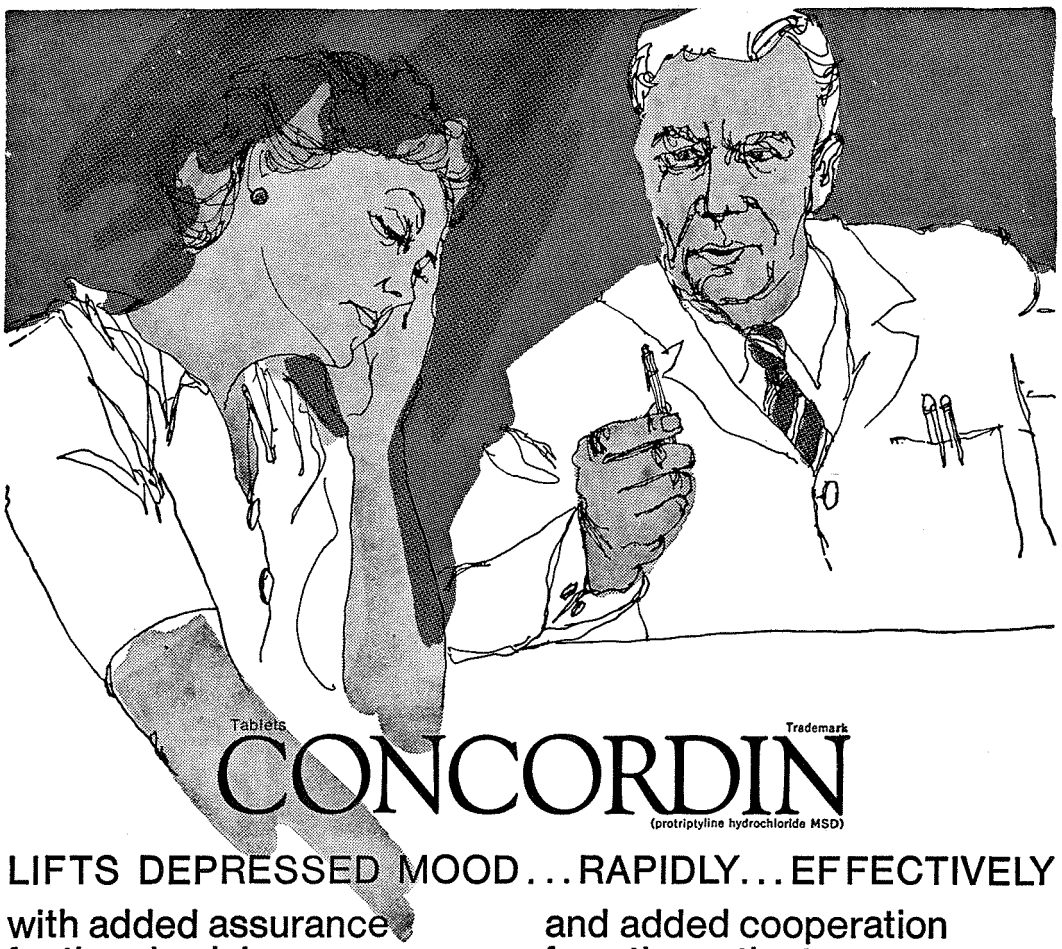

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- **Side effects infrequent and generally mild**...no evidence to date of renal, hepatic or blood damage

and added cooperation from the patient

- **Rarely causes drowsiness**...particularly appreciated by the ambulatory patient
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Supplied: Tablets CONCORDIN, each containing 5 mg. of protriptyline hydrochloride, in bottles of 25, 100 and 500. Tablets CONCORDIN, each containing 10 mg. of protriptyline hydrochloride, in bottles of 25, 100 and 500.

Note: Detailed information is available to physicians on request.

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MEDICAL SUMMER SCHOOL 1968

LAWRENCE V. ZRINZO

Health/Education Officer M.M.S.A. 1967/1968

The Malta Medical Students' Association this year has organized its first Summer School for local and foreign students. It consisted of lectures and demonstrations over a two week period. The first week was devoted to Surgery and Medicine, the second to Obstetrics and Gynaecology and Pathology.

The Opening Ceremony was held on the 12th August. The Minister of Health, Dr. A. Cachia Zammit, made the introductory speech. Professor Rodgers, of Queen's University, Belfast and Professor Scarborough of The Welsh National School of Medicine were present.

Prof. Rodgers lectured on Portal Hypertension and on the Tongue. The other two lectures were excellent: concisely yet most comprehensively, he talked on 'Post-Operative Care' and on the 'Treatment of Head Injuries'. The accompanying chart is the one he developed as an aid for the treatment of head injuries in his Surgical Unit. Prof. Rodgers rounded up his lectures by one on "Odds and Ends' which included such items as how much harm can be done by over anxious doctoring, leprosy and spina bifida. He also demonstrated a case of obstructive jaundice during the course of which he explained the pathogenesis of jaundice including the enzymatic deficiency diseases such as the Criggler-Najjar, Dubin-Johnson and Gilbert diseases.

Professor Scarborough lectured on the Natural History of Nephritis and on Pyelonephritis and Asymptomatic Significant Bacteriuria (A.S.B.) The last two lectures were on the two main types of Renal Failure viz. the acute, usually reversible, functional renal failure and the chronic, often progressive, structural renal failure. A stimulating issue was the real significance of the Blood urea level. The last lecture period was a discussion and, on student request, the professor explained the indications and contra-indications of the treatment of Hypertension. Demonstrations were on the 'Chronic Obstructive Airway Diseases' viz. Bronchitis, Bronchial Asthma and Emphysema.

On Saturday 17th August, Professors Scarborough and Rodgers were joined by Professor Pinkerton of Queen's University, Belfast, and Professor Hill of the Royal Free Hospital, London.

The students attending the Summer School met the four Professors at a Cocktail Party organized by the Malta Medical Students' Association. The local Professors in the Departments of Surgery and Pathology were present.

During the next week Professor Pinkerton delivered lectures on Urinary Tract Infection in pregnancy, on the Lymphatic Drainage of the Female Genital Tract and on Infections of the Vulva. His lecture on Placental Insufficiency was one of the best lectures we had, and encompassed the advantages and disadvantages of amniocentesis, the biochemical abnormalities of the amniotic liquor and probability of developing a useful investigation for the diagnosis of placental insufficiency based on maternal heat-stable alkaline phosphatase blood level. The period devoted to discussion was mostly occupied by an excellent review of Eclampsia and on the diagnosis and management of a case of borderline disproportion.

Professor Hill lectured on the course, types and effect of cirrhosis of the liver with special reference to viral hepatitis, primary biliary cirrhosis and active chronic hepatitis. One lecture was on Seneciosis and another on arterial degeneration. A highly valuable lecture was that on Cytodiagnosis, its uses, advantages and disadvantages over surgical biopsy and the criteria of malignancy in a smear.

Professor Hill also had the problem of ending this Summer School and he did this admirably. He gave us a most 'eye-opening' lecture on how much we tend to take too much for granted. He illustrated this with the help of line drawings, the falseness of depth perception with monocular vision and tales one of which ran: 'a missionary was accused by a cannibal of being a cannibal himself: if tins labelled with pictures of tomatoes contained tomatoes, tins labelled with pictures of babies contained babies; the missionary had a job explaining that the tins actually contained milk'. This indicates the importance of culturing a scientific attitude which after all, helps to keep up enthusiasm which is the prophylaxis against dull, boring routine work.

Medical Consultants at the St. Luke's Hospital also gave various lectures and demonstrations: Dr Rizzo Naudi gave a clinico-pathological demonstration on Familial Bleeding Disorders and on the complications of Paget's Disease of Bone; Dr. L. Vassallo gave a lecture on hypertension and one on the neurological complications of myxoedema and uraemia and on the diseases characterized by involuntary movements with special reference to Parkinsonism, Huntington's Chorea and Wilson's disease; Dr. F. Fenech also gave two lectures, one on the various modes of presentation of Bronchial

HEAD INJURY CHART

THE LEVEL OF CONSCIOUSNESS IS THE MOST IMPORTANT SINGLE SIGN IN CASES OF HEAD INJURY. IT MUST BE OBSERVED IN ALL CASES.

KEEP THE AIRWAY CLEAR

POSITION——The patient should be nursed on alternate sides, turning every two hours with the nose and mouth clear of the bed.

RESTLESSNESS—If the patient is very restless, padded side walls should be used, and the knees and ankles padded. Remember that restlessness is frequently due to a distended bladder. Protect the patient from injuring himself but do not hold him down by force.

SKIN——Turning two hourly and padding pressure points should be started from admission. Keep the skin dry.

MOUTH——Swab the mouth from admission, do not irrigate.

EYE——Protect the cornea by keeping the lids covered with saline soaked swabs.

FEEDING——If unconsciousness is prolonged for more than 24 hours tube feeding may be required. A fluid balance chart must be started. (Oesophageal tube No. 15 in the stomach).

URINE——Portex "layflat" nylon film tube gauge C may be used in the male. A fine self retaining catheter may be used in the female.

WOUNDS——Keep the wounds protected with a minimum of dressings and firm bandages. **BE ON THE LOOKOUT FOR OTHER INJURIES:**

CODING OF THE LEVEL OF CONSCIOUSNESS

0. Fully conscious.

1. Confusion (**1A**—Mild) Inattentive and depressed. Plausible and inaccurate statements.

(**1B**—Moderate) Answers simple questions, drowsy and irritable.
(**1C**—Severe) Almost inaccessible, may respond to commands.

2. Semi-coma **(2)** Postural tone present, no response to commands, eyelash reflex present. Urinary incontinence with reflex emptying. *Responds to painful stimuli.*

3. Coma **(3)** Postural tone lost, but decerebrate rigidity may be present. Pupils dilated and do not respond to light. Cannot swallow and will drown in own secretions if left flat on back. *No response to painful stimuli.*

Signs of increasing intracranial pressure:—

The pulse rate usually falls
The blood pressure usually rises
The temperature usually rises
The respiratory rhythm usually alters
A fall in the level of consciousness
An alteration in the pupils.

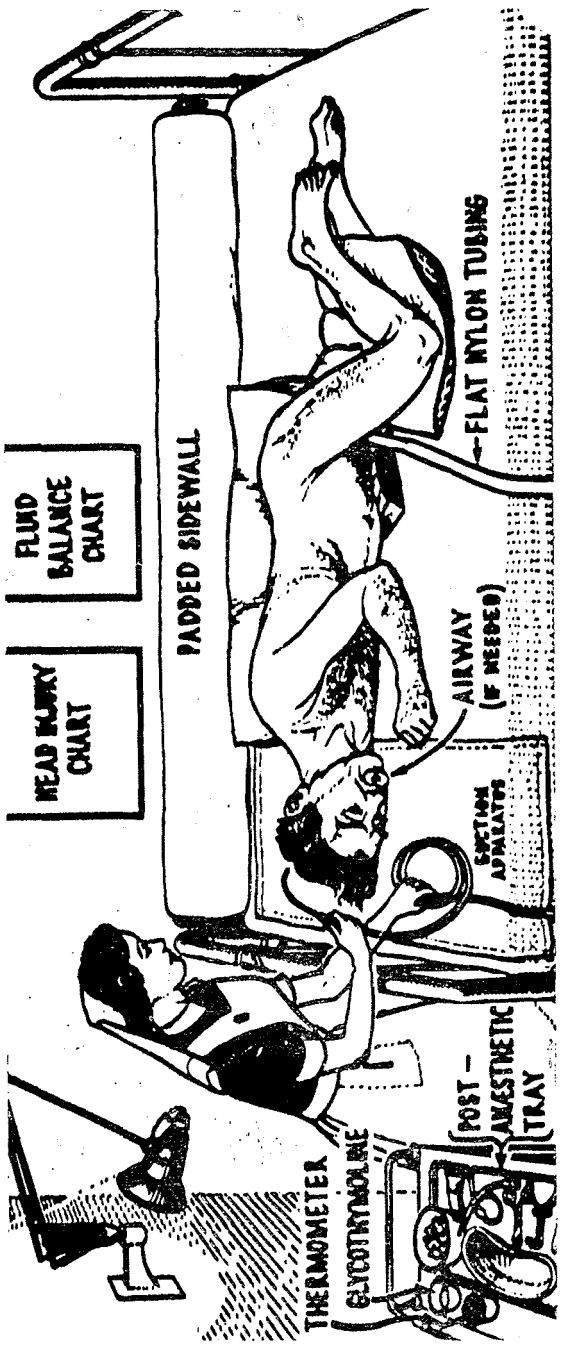
ANY RAPID ALTERATIONS OF THESE SHOULD BE REPORTED..

Carcinoma and on Myocardial Infarction. Mr. G.E. Camilleri of the Dentistry Department gave a lecture on the differential diagnosis of swellings of the jaw.

It was the first Summer School, but on the whole it was rather a success and for this we are indebted to the four guest Professors and the local consultants who took part.

We are also very grateful to the Minister of Health, Prof. V.G. Griffiths — Dean of the Faculty of Medicine and Surgery — and Prof. G.P. Xuereb for their constant help and encouragement.

We would also like to express our gratitude to Prof. A.P. Camilleri, Prof. A. Craig, and Prof. J.V. Zammit Maempel for the use of their respective departments.



MATHEMATICS

I have quite a lot of wishes;
Among them, my great ambition
Is to be a famous doctor,
And not a mathematician.

Hosts of formulae and problems,
Each sunrise brings more and more:
At the end of a Maths. Lecture,
How I stagger for the door!

Permutations, combinations,
Sines and cosines by the score;
Tan squared alpha, Cos squared beta,
Cube root eight and square root four!

Every day I have to tackle
Work which I strongly detest:
Dakin, Porter, Durell, Tranter-
All against me, at their best.

I try hard to concentrate me
At the work before me laid,
But my mind is twisted crosswise,
And no progress, none, is made.

In my mind a place is vacant,
I know, for all science topics,
But Maths, is not here included:
Why, I'd prefer reading comics!

A whole year of mathematics...
Makes me scream and tear my hair!
What if I should fail my finals?
Mummy! That would be a scare.

The whole prospect is so fearful
That I dare not meditate:
I'll be ready, calm and cheerful,
And reconciled to my fate.

VICTOR E. SAMMUT

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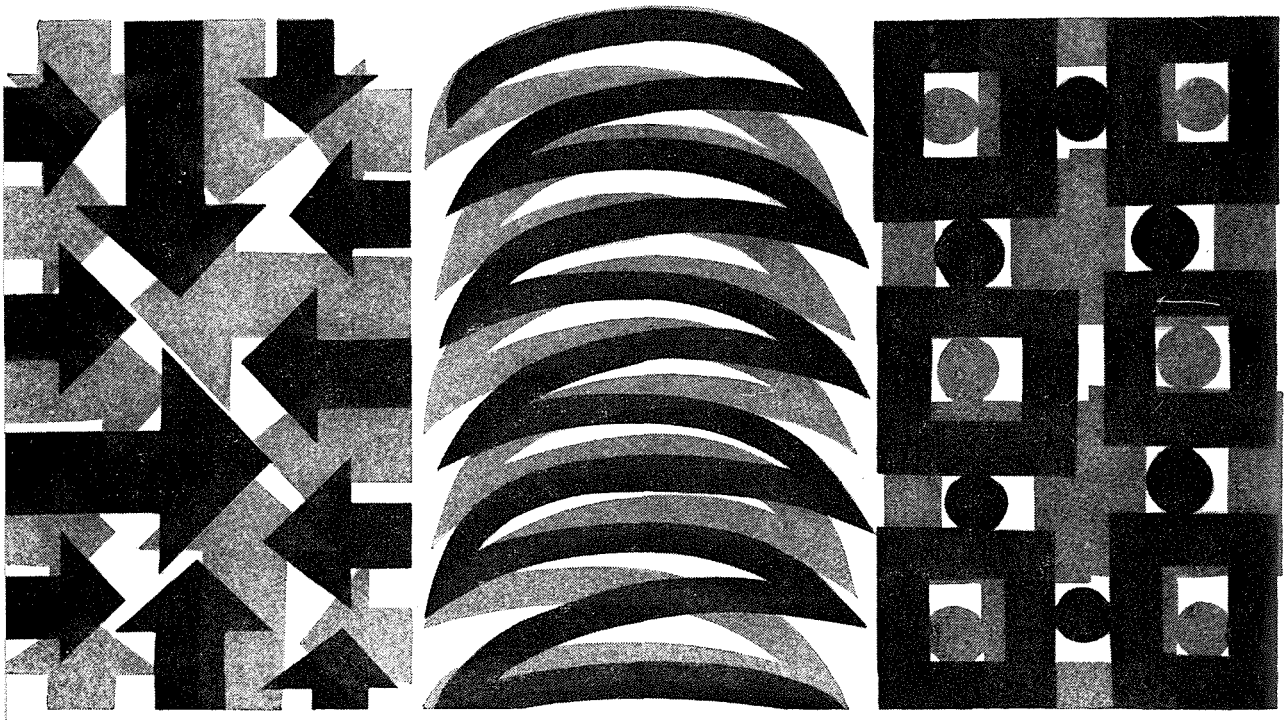

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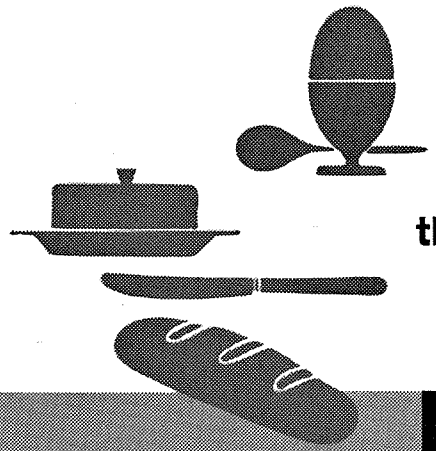

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triple effect

for digestive disorders
of various origin

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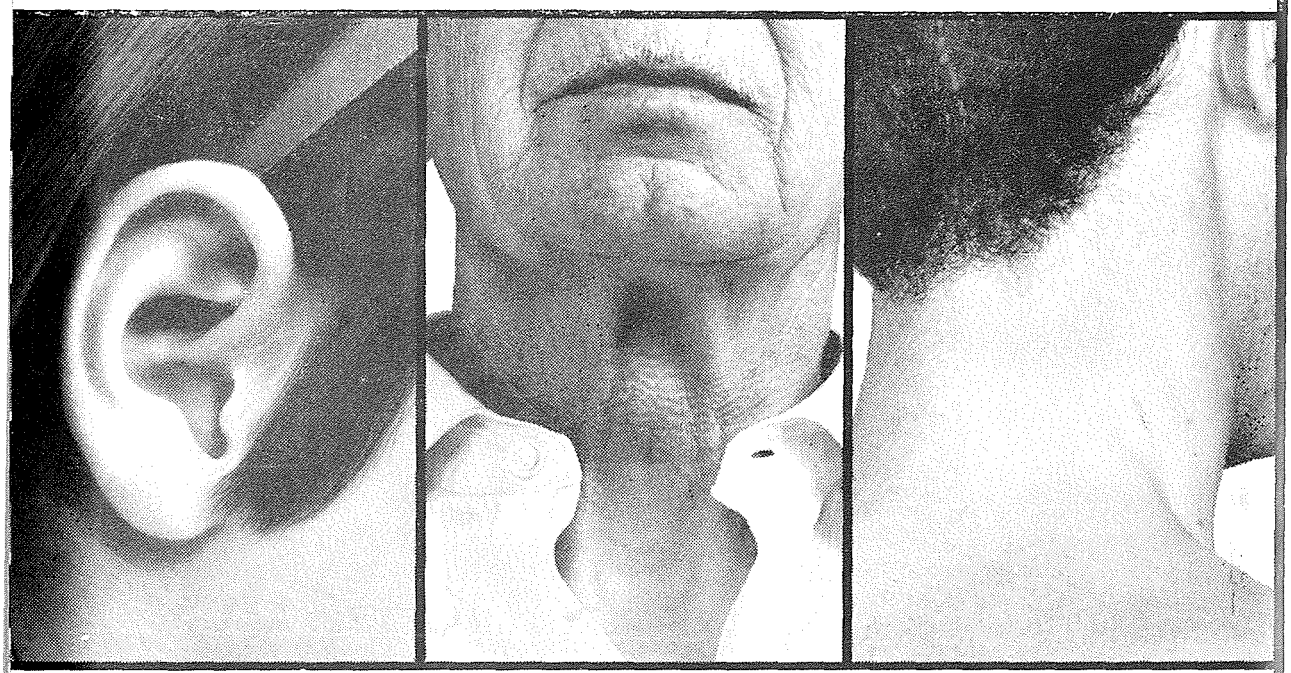
ORBENIN works here... ...here... ...and here



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Unlike tetracyclines and sulphonamides Orbenin is bactericidal; it *kills* bacteria instead of merely arresting their growth. Bactericidal activity minimises the risk of relapse.

. . . strep. and pneumococci . . .
Orbenin is bactericidal against the common Gram-positive pathogens—streptococci, pneumococci and staphylococci, including strains resistant to other antibiotics.

. . . and more staph. than any other antibiotic . . .
Because Orbenin is bactericidal and stable to penicillinase it is able to kill penicillinase-producing staphylococci—the penicillin resistant strains.

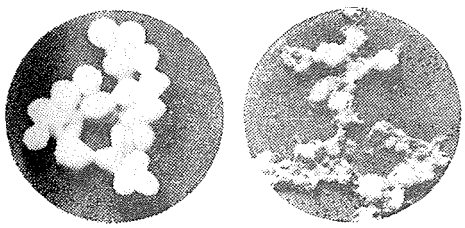


Photo-electronmicrographs, magnified, showing cells of Staphylococcus aureus phage type 80. These typical penicillinase-producing organisms are illustrated before and after exposure to a therapeutic concentration of Orbenin (cloxacillin sodium B.P.).

Indications: Otitis media, Tonsillitis, Pneumonia, Empyema, Boils, Furunculosis, Abscesses, Osteomyelitis, etc.,

Orbenin* (cloxacillin sodium B.P.) was discovered and developed by **Beecham Research Laboratories,** Brentford, England.
Distributors: Joseph Cassar, 207-208 Old Bakery Street, Valletta.

REPORT OF THE ROYAL COMMISSION ON MEDICAL EDUCATION-A REVIEW

FRANK G. PORTELLI
President M.M.S.A. 1967/1968

The Royal Commission headed by Lord Todd has endeavoured to produce "a picture of the likely pattern of Medical Education in the future". Not since the Goodenough Commission (1942-44) has the subject of medical education been so thoroughly reviewed.

IMPORTANT CONCLUSIONS were:

1. Absence of adequate arrangements for postgraduate training has led to retention of obsolete concepts on undergraduate medical education.
2. That the aim of the undergraduate course should be to produce an educated man who will become fully qualified only by postgraduate training.

The objectives of the clinical course can only be achieved if the curriculum is less congested. Teaching should be aimed at providing a *basis* for the understanding and treatment of patients.

3. That there should be no sharp dividing line between preclinical and clinical studies, indeed, that they should be amalgamated. But, they advocated that the length of the course should remain unaltered. The preclinical course should preferably be a broad medical science course itself leading to a degree. Students forced to abandon their clinical studies could then immediately take up a career in a para-medical field.
4. Students should be assessed by careful reviewing throughout their period of study. These assessments could be supplemented by a final test if it were needed to resolve any doubts about the class of degree. Students would then be constantly aware of their progress.

STATISTICS

The purpose of teaching statistics to medical students is not to produce statisticians any more than the purpose of teaching biochemistry is to produce biochemists; it is to help Doctors think quantitatively.

SEX EDUCATION

This has to be included if the doctor is to understand and help his patients.

GENERAL PRACTICE

Students must be given an insight into this; for patients in hospital are not average patients but a highly selected group, forming only a small percentage of those seen in general practice. Elective periods may be spent by students attached to selected general practitioners.

ADMISSION TO PRECLINICAL

The tendency to regard "A" levels in Chemistry, Physics, and Biology as the only acceptable qualifications should not be accepted without question. The "A" level standard, at least in Chemistry, is higher than is required for embarking on a medical course.

A rough estimate on the cost of education of a medical student is given as £10,000, excluding capital expenditure for erection of buildings, etc., and grants to the student.

MALTA

A proposal by the Malta government at the Commonwealth Medical Conference in 1965 to expand the medical school of the RUM to take up to 15 students from UK and 25 local students per year, was studied with "particular interest".

It is considered to be basically sound. However, the (UK) Department of Education and Science was unable to give grants to Overseas universities, and the Ministry of Overseas development could not subscribe the education of students normally resident in Britain.

The matter has been referred to the Ministry of Overseas Dvelopment to help with the expansion in the most effective way. It is interesting to note that the authorities normally responsible for supporting students in Britain are unwilling to meet the cost of educating a Medical Student in Malta even though this is much lower than educating him in Britain.

A sample of the numerous tables and charts contained in the Report is given below.

PERCENTAGE OF STUDENTS WHO PASSED FINALS AT FIRST ATTEMPT

	1963/64	1964/65
Charing Cross	76%	77%
King's	85%	63%
Royal Free	69%	85%
Barts	75%	69%
St. Thomas's	77%	73%
U.C.H.	71%	68%
Guy's	70%	61%

Average number of students of all London Medical Schools who passed finals at first attempt — 84%

IN CONTRAST

St. Luke's Hospital, Malta, 1967 — 30%

PERCENTAGE OF STUDENTS NOT KNOWING WHAT WAS EXPECTED OF THEM:

Year of course (1966)	
1st. clinical	36.4%
2nd. clinical	28.6%
3rd. clinical	11.6%

PERCENTAGE OF STUDENTS PERFORMING PROCEDURES

Procedure	Never	More than once	Once
Stitching wounds	5.4%	92.1%	2.5%
IV injections	12.2%	82.6%	5.2%
IM injections	22.6%	68.6%	8.8%
Passing of catheters	29.2%	55 %	15.8%

STUDY HABITS

	Average hrs/day	Proportion passing all exams. first attempt.
Study every day, fixed times	2.89	74.6%
Every day, no fixed time	2.36	62.1%
Once or twice a week	2.48	69.8%
Sometimes intense, sometimes nil	2.58	—
Intensive study before exams.	2.91	54.3%

MISCELLANEOUS

THANK YOU

As a first year clinical student, I am sure that I speak on behalf of all my colleages when I say "Thank you Dr. Tony Busuttil for your tireless efforts during our Bacteriology practical sessions last year."

Dr. Busuttil's constant slave-driving and excellent method of teaching slowly but surely drummed into our thick heads the important points of Bacteriology, and just how effective these practical sessions were is evident from the fact that all the course passed the Bacteriology Practical Examination in June. I can honestly say that we learned most of our Bacteriology during these weekly encounters with the "Busu."

We are very fortunate to be having Dr. Busuttil with us again as a demonstrator in our clinical course.

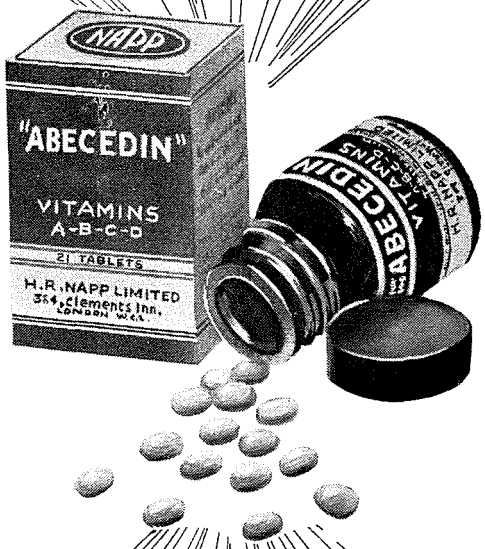
So "Grazzi Busu, we all appreciate your efforts even though at times we do not show it."

PASTERELLA.

Malta Junior Chamber of Commerce

A junior Chamber of Commerce is being formed in Malta. Its aim is to bring together young men and women who occupy, or are being trained for, responsib'e positions in the community. University students are strongly urged to join. A fee will be charged. Further details from George Depasquale and Alex Felice.

"ABECEDIN"



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VITAMIN DEFICIENCY

NAPP

CLASSICAL ETHICAL PRODUCTS

A MODERN DEPARTMENT OF ANATOMY

By

J.L. PACE

Lecturer, Department of Anatomy,
Royal University of Malta.

The new Anatomy Department of the Royal University of Malta at Msida is nearing completion. In design and equipment it has been modelled on the Department of Anatomy at the Middlesex Hospital Medical School in London — perhaps the most modern and well-equipped department of its kind in the British Isles.

Completed in 1960 ,the Anatomy Department at 'The Middlesex' includes a lecture theatre, a museum and teaching and research laboratories.

The lecture theatre seats 60 students. It is equipped with 4 closed-circuit television monitors and a two-way intercom system. This provides for live television demonstrations from within the Department itself as well as live transmissions with sound commentary directly from the Hospital Radiology Department.

The Histology teaching laboratory (Figure 1) accommodates 80 students.

The dissecting room (Figure 2) has an area of 2800 square feet and is provided with 18 tables. Dissected museum specimens are displayed along the walls and are readily available for reference during dissection. Adjoining the dissecting room is an embalming room, a tank room, a well-equipped workshop and storage rooms.

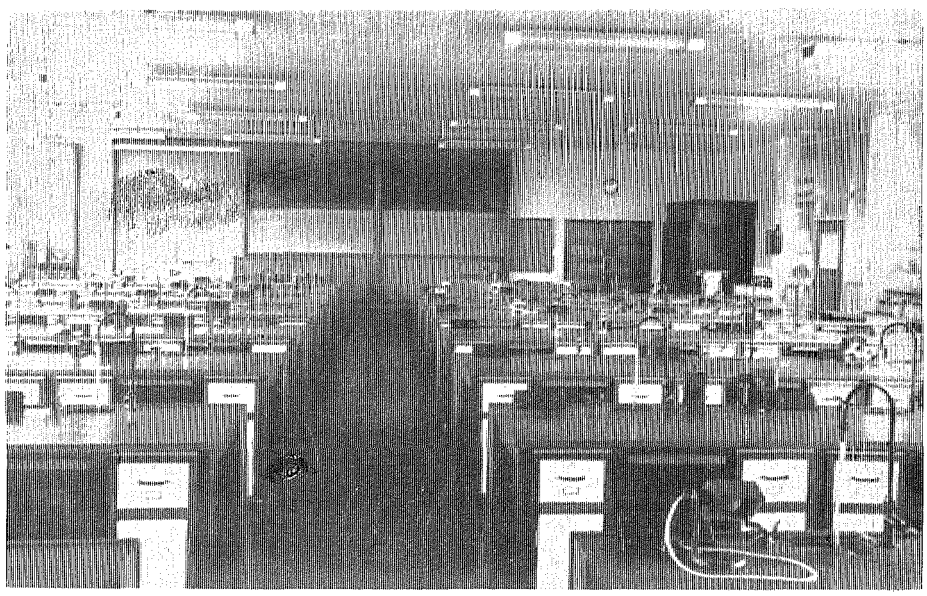

Fig. 1. THE HISTOLOGY TEACHING LABORATORY

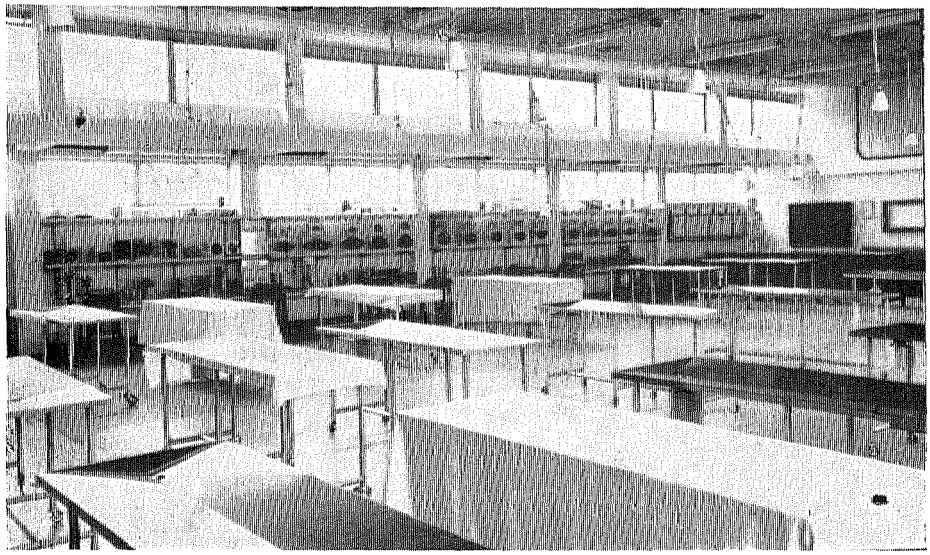

Fig. 2. THE DISSECTING ROOM

The Living Anatomy room contains 4 examination couches. It is equipped with various clinical instruments (ophthalmoscopes, otoscopes, etc), muscle stimulators and x-ray viewing boxes. Adjoining it are two tutorial and a demonstrators' room.

The museum (Figure 3) displays dissected, cross-section and anthropological specimens. A 24-panel x-ray viewing box and a collection of normal radiographs (with accompanying labelled outline diagrams) are provided. One side of the museum is used as students' studying space. Furniture and specimens are easily movable making it possible to convert the museum into a committee room when the necessity arises.

The research side includes an Experimental Embryology laboratory, a Histology research

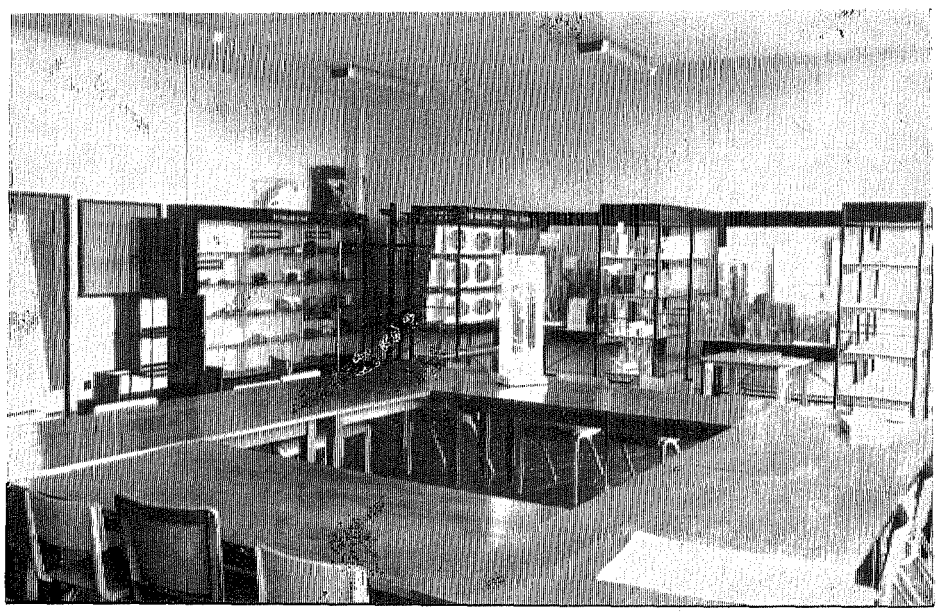

Fig. 3. THE MUSEUM

laboratory (Figure 4) and preparation room, an animal operating theatre (with B.P. and E.C.G. monitors), an adjoining recovery room, an animal post-mortem room and quarantine rooms. There is a photographic studio and processing room equipped with the most up-to-date photographic and microphotographic equipment, an x-ray room, and an electronmicroscope laboratory.

My thanks are due to Professor E.W. Walls, Courtauld Professor of Anatomy at the Middlesex Hospital Medical School; also to the authorities of the Middlesex Hospital Medical School for permission to publish the photographs.

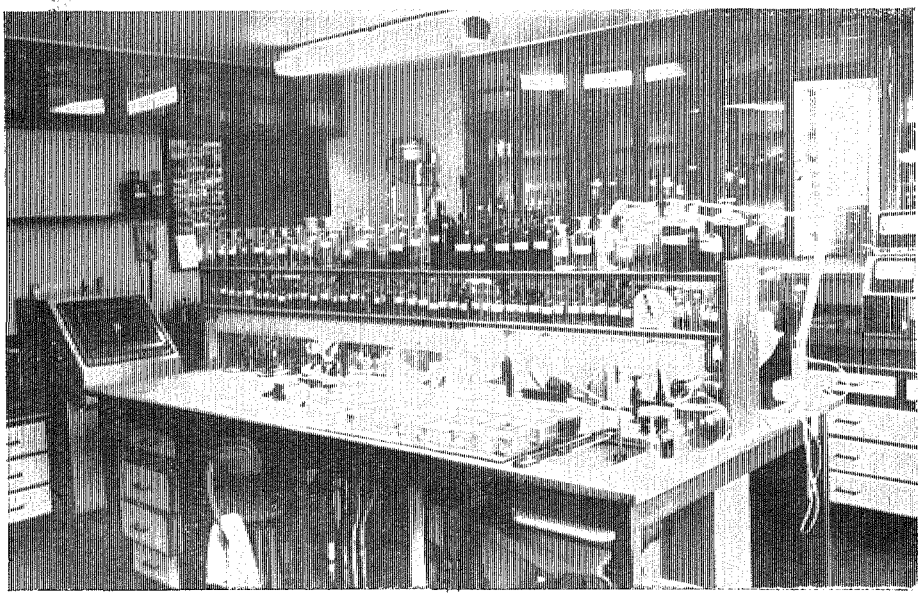

Fig. 4. THE HISTOLOGY RESEARCH LABORATORY

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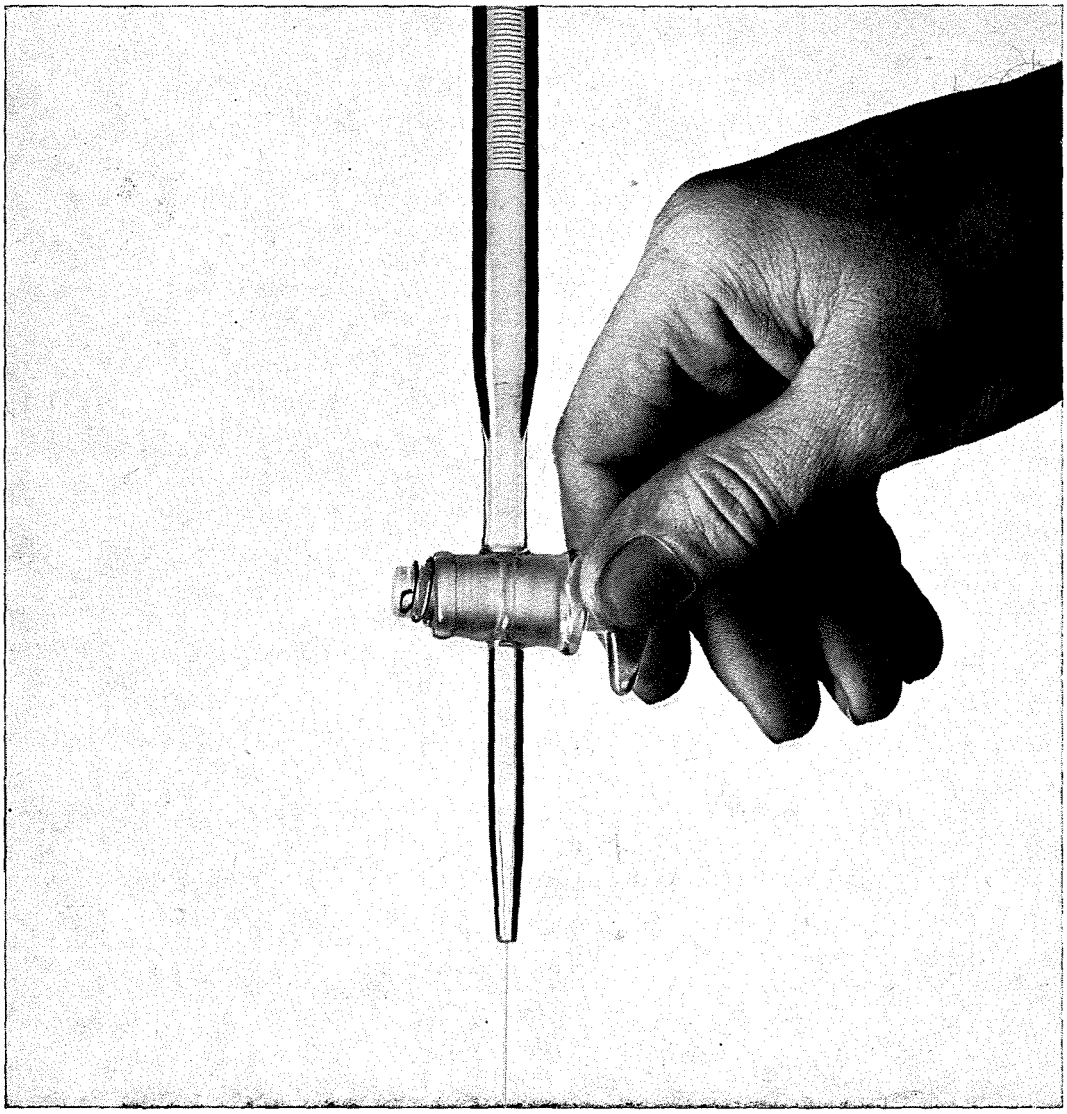

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AH..... THESE DAYS! !

Zzzz — a quick snore, now stretch and yawn
"What? 'tis seven, when comes the DAWN?
Alas there's scheduled a lecture at eight
In few minutes hence, I'll be abominably late."
Student forlorn
In this early morn..... Poor me!!

Short stature, bald pate, — slightly burly
The epitome of precision and inevitably early
In he comes, jaws a chewing, an eye in half wink
Lectures one hour, and with ne'er a blink
"Tumours", he says, "are removed by the roots
No need for worry
Rush nor flurry
Just don the black boots".

Figure tall and lean, with temples graying
Fingers with pull-cord continuously playing
Whose degree of magnitude
In surgical exactitude
Makes me worry and wonder
Then pause and ponder
.....Woe is ME!!

B A N G! reports the well aimed gun,
" B E H ! " — the hunter cries
"Inter Alia!" — now, that hunted one
In gushing blood now lies
"GENTLEMEN, I thought you knew that marks accrue
For very few
The better the shot
The better your lot".....
The ides of June are nigh!
Beware!" — Ah me, oh my!!!

Let us pause to see
His musketeers three:
One pivots and fidgets then scratches his topper
Now belches the diagnosis, forthright and proper
The other short, bespectacled with high-stepping gait
Calm, methodical and compulsively late
The third generous in girth with unchanging expression
"Tell me", asks he, "of therapeutic aggression".

"Various views you will all hear expressed
But midwives and students... my words are your text".
NEAT, petite, poised a-front of the desk
Where his fingers design a musical complex
"Mother in labour, with placental delay.....
What now? NO SIR! Never CREDE".
Ah... indeed I daresay.

"We, now do think in terms....."
Of death, disease and causative "worms"
Yes, yes indeed, in eye-rolling splendour
A flicker of fingers twixt arms we do gesture.
Now its the hour, ELEVEN! that's it
Sit yourselves down for a session of wit!
One after another in picturesque slide
"Now... ahh... who... aahh... shall be my scribe?"

Biopsied dissection of this "pot pourri"
Tells how charming, how sweetly and calm did she.....
Use the water of life to embalm De Gru.....chy.
Add two drops of urine, plus a chemical or twain,
He'll "fight" out his point, true to his name
"Closely observe head to foot and entrails
Ah me, you shall learn..... DEAD MEN TELL TALES!!"

"Yes, I mean NO, rather yes and no"
My decision could well be "maybe so"
"Now, that word — is it Greek or Latin
Who can tell me, its origin?"

But alas! this shall not be for mere monarchs and men
Lest there be MICROBES to soil this my pen
His lexicon manual makes his language so actual
With precision in practical and historically factual
.....Indeed a formidable fellow!
Thus runs my story
In detail and glory.
"Now "x'se naghmlu"
Which states — what shall we do?
From eight until five
We're just kept alive
By lectures and walks
Gestures and talks
Such a routine and this always
Ah me, oh my these days!!!"

by SAD SACK.

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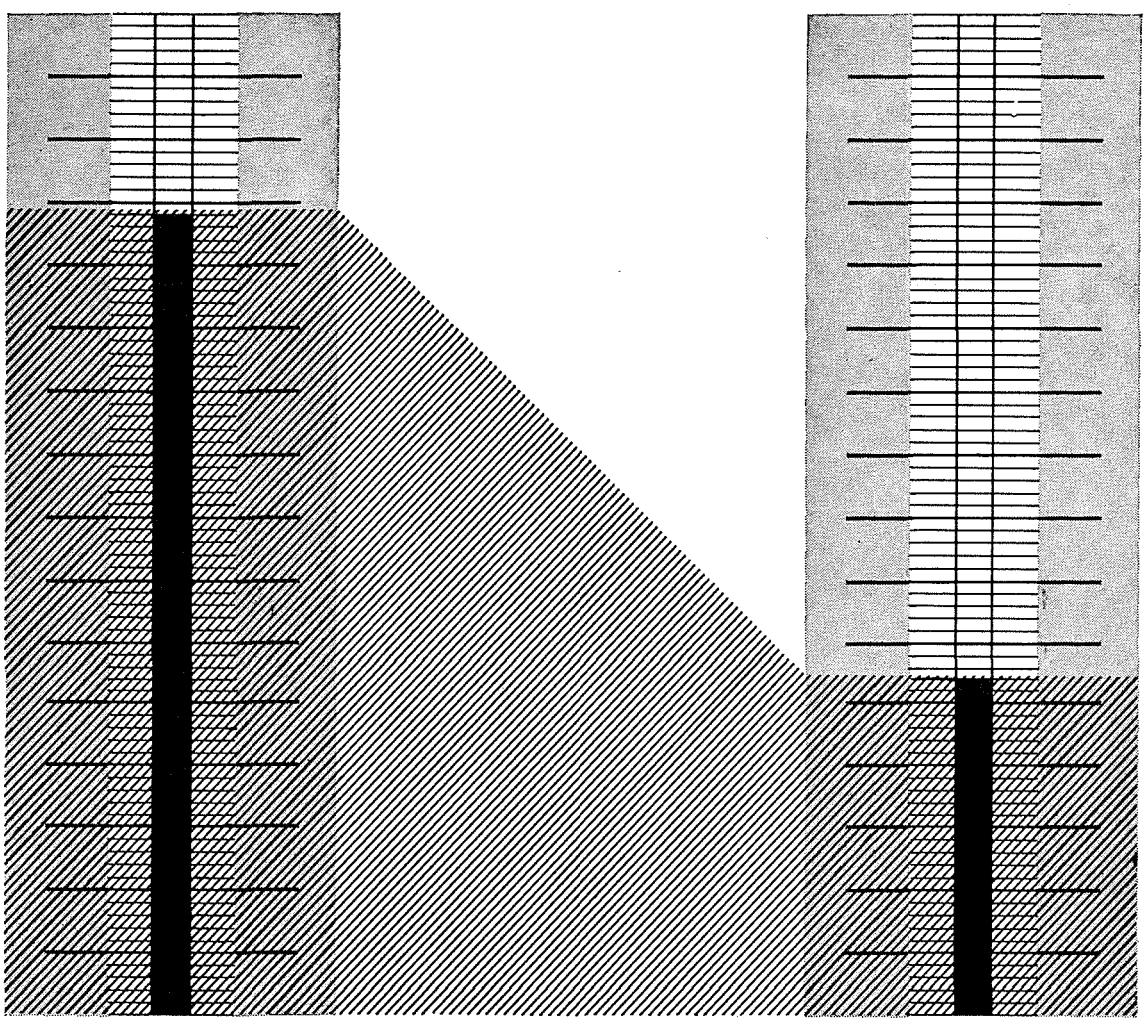

GASTRIC GRAND PRIX

P.R. (Sheepskin coat, holding sigmoidoscope and microphone).

Good-afternoon. This is Pete Rumble reporting the start of the Gastric Grand Prix; and here at Silverstool it's a fine sunny afternoon, though perhaps a little windy. There are five cars taking part this afternoon, we have the supercharged sennapod with Roy Casteroilli driving, some of you may remember how earlier this year in Germany he positively burnt up the Nurburg ring. Next to him on the grid is Kellog in the All-Bran and next to him Syrpor de Figura driving a new car from the Cooper-Lotus Assembly, the Cooper-Flatus. Then in the second row are the two famous intercontinental drivers Mucosa in the gut wall special and Cascara in the British designed BMR — Now I hand you over to my colleague Toby Belch to describe the start. Come in Toby.....

T.B. Everybody's ready now and the expectorant crowd are hushed as the starter makes a motion with his chequered flag, and they're off; and straight away Cascara goes into the lead closely followed by the All-Bran and all the others huddled into a bolus. As they shoot round the lesser curve, past the gastric pits, they're heading for the dreaded pyloric chicane, a twisting left hander. But they are all through safely and coming up now to the first duodenal hairpin. Some drivers are very nervous at this stage, things have been known to go vagally wrong here; but they are all through. No, wait a moment Kellog's out of control in the All-Bran, his steatorrheaing wheel has broken — the trouble with him — All-bran and no brains. And now as they disappear into the distance, I'll hand you back to Peter Rumble.

P.R. The track's pretty deserted here, nothing much happening, just a few polyps pottering around, that's all. Ah, here they come and it's Cascara in the lead, but the Gut-Wall special is moving with tremendous omentum, he's intestinal hurry. They pass the ground staph at a breakneck speed and Cascara is going to have to constipate really hard at this stage. Oh! Cascara's skidded, yes he's skidded on a Peyer's patch and shot right up the appendix. He only just missed Harry Caecum. The rest of them are going off now to the concealed hepatic flexure where Toby is waiting in a lymphnode; I'm off to the finish, so back to Toby...

T.B. And here they come into this very sharp bend. It's the flatus and BMR battling it out Traditional old enemas these. And Casteroilli, with his lightning refluxes is driving at a metabolically fast rate, at least 100 piles an hour. But wait a minute, his windscreen has just been shattered by a gallstone, he's swerved right off the tract and up the inguinal canal, he must be in diarrhoea trouble, all I can see from here are a few peristaltic waves lapping gently over him. I can't see the finish so I'm going to hand you back to Peter Rumble. Come in P.R. ...

P.R. Well I'm standing on a stool, to get a better view and as I look through my sigmoidoscope I can see them coming around the final bend and it's still Cascara, No, No, we've just heard he's dropped out with a filling defect which he failed to rectify, but it's nothing serious. So now, unless there's a pile-up at the bottom there's nothing to stop the flatus. Yes, the flatus is coming in, what a triumph for British effort. There's his dusky girl friend Melaena flushing proudly as he eases past. So after all the days of strain the flatus passes out tops proving that in the final analysis, as they say, it takes guts to win. And the Silverstool crowd, full of smiling faeces, cheers him wildly. As the leaders flush past the stand for the final time one must salute their bravery for coming through it all quite undeterred and without a trace of a motion on their faces.

St. Thomas's Hospital Christmas Show
Dec. '67.

Bactericidal antibiotic for urinary tract infections

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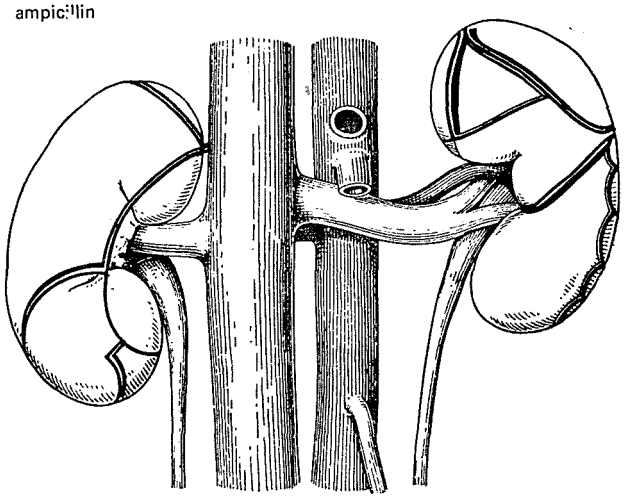

treats the acute; prevents the chronic

The majority of drugs available for the antibacterial therapy of urinary infections are bacteriostatic. They suppress bacterial growth but do not kill the organisms. In some cases the natural body defences are themselves capable of clearing the stunned bacteria, but in many others, even after prolonged therapy, sufficient viable bacteria remain to cause a focus for continual re-infection.

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THE COMMUTER FACTORY

28th June 1968. It is Friday, the fifth day of our national rail dispute. That is what they call it. Not a strike, not a go-slow. Simply a calmly calculated collusion of several thousand railwaymen refusing to do overtime or rest-day work. At a time when Britain is trembling at her knees, begging for a heavenly harvest she can sink her teeth into, praying for a productive climate in which she can extricate herself from the frightening debts she has stockpiled — and make no mistake about it, she has nailed her debts to a treadwheel. The utter failure of devaluation whispers this fact to the hills — at a time like this, her city-workers are queuing four-deep on the platforms twenty miles from their offices, her roads are choked and her vital export orders sit rotting in their yards. This is no dispute, it is blackmail; petty blackmail by which an otherwise insignificant section of the community has paralysed the power of its government. Perhaps it is a symptom of the moral lethargy to which a nation showered by social benefits has sunk. Perhaps so, but it also demonstrates far more fundamental principles about the city-dweller as distinct from the island-dweller, such as the Maltese, who is far less concerned with travelling and when he is concerned conducts it at a leisurely 'civilised' pace. (Malta contains three hundred thousand inhabitants, measures 17 miles from tip to toe and owns only two sets of traffic lights). It might be of interest then to consider the possible effects London travelling has on the London soul.

(1) We have already seen the direct effect of disruption to a city's travel services during the last five days; the discomfort, the delays, the frustration, the general impedance to the smooth-running efficiency and total work output of several million commuters. The indirect effect has yet to come; the lost export orders will be reflected in the Londoner's Budget next March.

(2) Next the situation given that normal services exist:- The good Doctor Johnson once remarked, "Sir, when a man is tired of London, he is tired of life; for there is in London all that life can afford". Dr. Johnson's remark was made in the eighteenth century; two days ago London Transport announced that minimum fares on its buses would rise to 5d for one mile and 9d for two. (The distance from Valletta to Birżebbuġa is 7 miles and the fare 7d). The good doctor's remark was made at a time when travel was conducted in a sedate sedan; at a time when rush-hour was generally taken to mean a barbaric land east of the Urals pronounced through a cornedbeef sandwich. He was a fortunate man, he never knew the agonies of Waterloo. Here at this famous London sportsground between 1630 and 1830, the natives daily reenact that glorious battle. The men in the peaked caps holding the gates represent the thin line of Wellington. The delirious horde, seething, surging, shrieking obscenities, stabbing wild stabs with wicked steel-pointed umbrellas, represent our brothers from across the Channel. The object is to scale the barriers; if you can board the train on the far side as well, you are a true-blooded Londoner and have done all the duty England can expect of you. It is only one scene of many, but one to moisten your eyes. We call it the rush-hour.

(3) Given the situation exists, what are its effects?

Traditionally the Englishman has a stiff upper lip, an air of reserve, a tolerant outlook on life and a love of blood sports and fair play. Examine these one by one and you will find that they are all in effect protective phenomena against his environment and nowhere more highly developed than in the city commuter. Any who doubt Darwin's ideas on the survival of the fittest or the development of protective mechanisms in a species has only to purchase an 8d ticket to London Bridge for the cheapest conversion on the market. Take the evening paper for instance. This phenomenon never contains a halfp'orth of news or gossip which the Londoner has not already heard earlier in the day. Yet there are few who can resist the groping reflex — the fourpenny grope as they pass the newstand — because they know a paper is invaluable. It is a curtain to withdraw behind, safe from their fellow passengers. Experience has taught them this; it is a conditioned reflex. In much the same way as lower creatures employ landscape colours to camouflage them or shells to shield them, so the commuter wraps himself in his newspaper. Those who do not regard this adaptation to an environment must compare it with the Maltese bus where the atmosphere is one of communal endurance rather than of self-survival and papers hardly exist.

(4) The comparison is striking and is of value, because it hammers home the point that the more complex we make our society, the more man becomes subject to the forces around him and the more he is driven to resemble the animal herd. This of course leads on to the question that if man is derived from the animal herd, is civilisation (here illustrated by city travel) taking him further away from it or bringing him back? In other words, does civilisation as we know it imply both human

and material progress or merely material *progress* and human regress?

The greatest number of live bodies I have witnessed in a railway compartment designed for twelve is twenty-six. That occurred one cold December morning after an unexpected fall of snow. For the past five days a handful of our fellow beings have deliberately inflicted the same scenes on us again. But the most alarming part of it all is not the deliberate infliction, but the startling fact that these stifling tumbrils, which rattle into the great London termini stuffed like cattle wagons, bear an unmistakable resemblance to our battery chicken farms. Much has been written on the evils of the battery chicken farm, the rows of brainless birds who live and then die without seeing the light of day, but I have yet to meet a chicken, roast or socially, who would exchange his inhuman lot for the Charing Cross line. At least chickens don't pay to be stuffing for a conveyor belt; they don't even have to face the return journey.

So perhaps we ought to ask ourselves, are we really no more than servants to our environment even though we have created it, no more than city-food for Darwin's theories, no more than lonely animals in a herd? Perhaps we must also remind ourselves that as yet Malta has no cities, no trains, no rush-hours, BUT THE TIME IS DRAWING NEAR. The new university is almost complete, ready for a new generation; the hotels and villas in St. Paul's Bay are almost ready to face the tourist wave. Perhaps it will not be so long before we hear the porters shout: *"Roll up, buy your ripe commuters 'ere! Fresh today, luverly commuters two a penny!"*

R.A. LOMAX

Guy's Hospital,
London Bridge. 28.vi.68.

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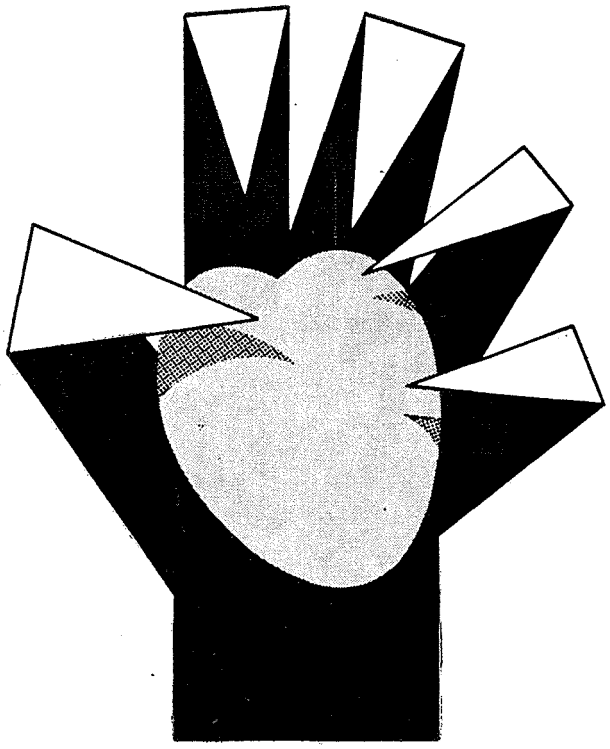

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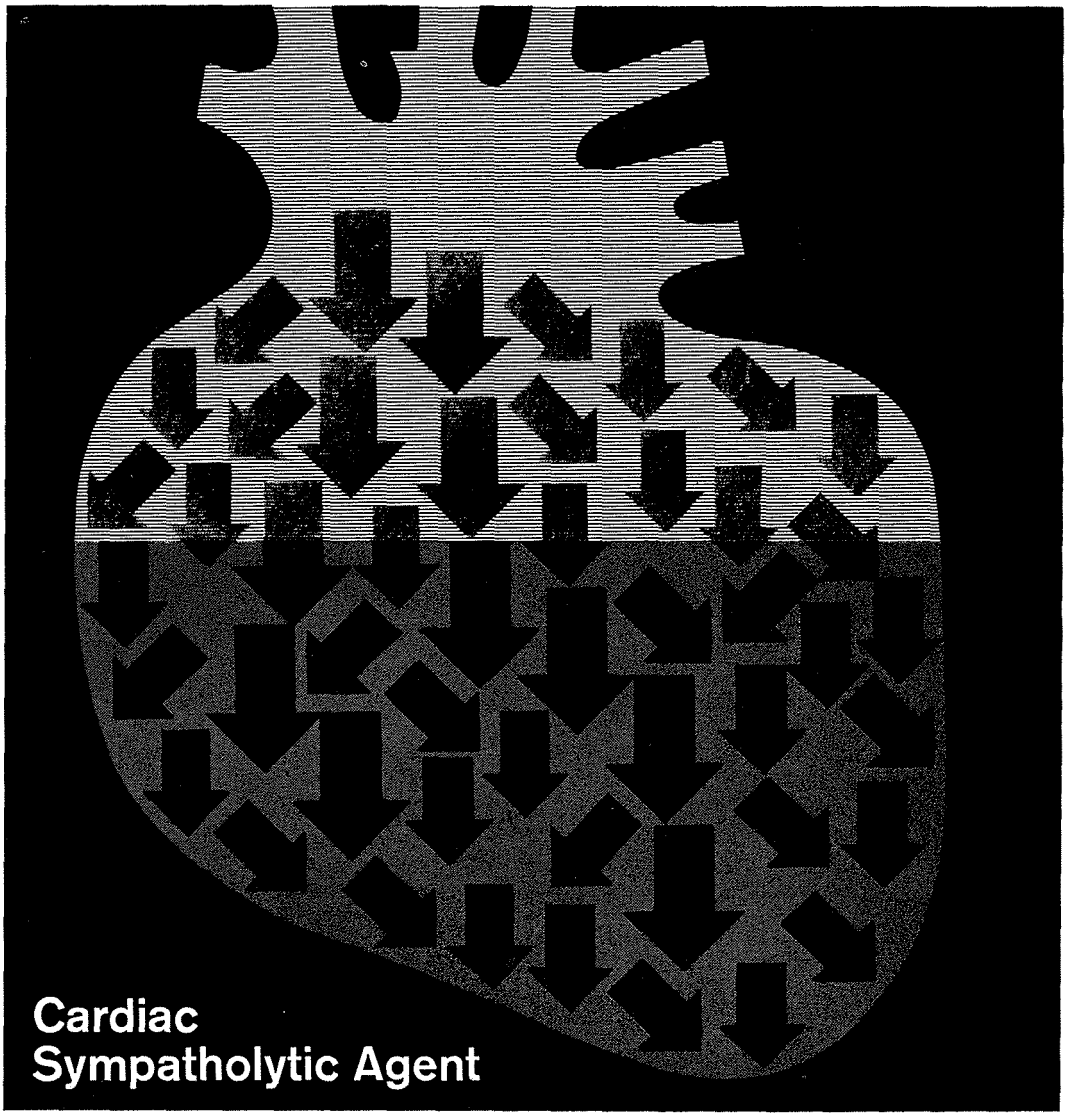

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THE MENSTRUAL CYCLE IN THE NORMAL HUMAN FEMALE

ROBERT FARRUGIA RANDON

GENERAL

The menstrual cycle is a sequence of morphologic changes in the reproductive system, particularly of the endometrium, that culminate in an episode of uterine bleeding. The cycle may be regarded as consisting of three phases: (a) proliferative (b) secretory (c) decidual or desquamative, but desquamation is more generally included in the proliferative phase. Typical length is twenty-eight days. Clinically, cycle ranges from twenty-five to thirty-one days and this is accepted as normal. It has, however, been found that only 53% of cycles may be expected to fall within this range. The question when exactly in the cycle ovulation does take place is an important one, and will be reviewed briefly after the description of the cyclic changes occuring in genital sites have been fully dealt with.

CYCLIC CHANGES IN THE FEMALE REPRODUCTIVE SYSTEM

The Uterus: It is the uterus which undergoes the most important changes during the menstrual cycle. The changes involve the myometrium, endometrium and the blood-vessels supplying the uterus. These changes will be described in turn:-

(a) Changes in myometrium:- During the last ten years or so, myometrial activity in the human has been much studied by the aid of intrauterine balloons (1). At the University of Georgia this question has been thoroughly investigated with the aid of pressure tracings and electro-uterograms. Balloons fastened to short sections of urethral catheters were placed in the uterus and cervix and then connected to Hamilton optical manometers (2, 3). The manometers and balloons were fluid-filled so that transmission of uterine pressure changes to manometers was accomplished by displacement of less than 0.01 cc. of fluid even when pressure-changes as large as 400mm Hg. occurred. Accurate tracings could be obtained with less than 0.1 cc. in balloon though usually 0.2-0.5 cc. was placed in cervical balloons and 0.5-0.1 cc., in uterine balloons. Pressure tracings obtained with small intra-uterine balloons seem superior to the electrouterograms. It has been found that during the proliferative phase contractions of the uterus are frequent and of small amplitude, whereas during the secretory phase the frequency diminishes and the amplitude increases. Downward from the dome of the uterus the contractions and relaxations of the muscle fibers become progressively more frequent and this presence of different pressures in different parts of the uterus allows during menses the downward propulsion of the menstrual debris towards and out of the cervical canal. During the relaxation phase there is a large pressure gradient between the lower uterine segment and the cervix and this propels the debris into the cervix and ultimately into the vagina. Therefore during the relaxation period the menstual debris is pushed down towards the lower uterine segment and during the contraction phase the debris is pushed down through the lower uterine segment into the cervix and lastly into the vagina. It has been found that Pitressin, and Neosynephrine increase uterine activity on injection. In some patients small doses of adrenaline have decreased the uterine activity. It has to be borne in mind also, that during the pre-ovulatory phase the myometrium becomes soft and spongy.

(b) Changes in endometrium and its blood supply (4):- In the early estrogenic phase there is proliferation of stroma and endometrium. Mitotic figures can be seen in the gland and stromal cells. The spiral arteries reach the surface. The outer and inner coats of the arteries are very thin and the middle coat consists of two to three layers of smooth muscle cells. The capillaries run parallel with the surface and the new capillaries are simple endothelial tubes. The veins also run parallel to the surface. These unite with the venous stems which run at right angles to the surface. These venous stems are thick walled. It has to be noted that the veins also undergo cyclic changes during the menstrual cycle.

In the late estrogenic phase the endometrium is some 2-3mm. thick. The cells lining the surface and glands are mostly columnar and contain a little glycogen. Most of the cells are mucus secreting. During the phase of endometrial proliferation the epithelial cells exhibit marked phosphatase activity, particularly at their free borders and in the cytoplasm apical to the nuclei. The secretions in the lumina contain much phosphatase. The spiral arteries during this phase increase in length. The adventitia is thick and the inner elastic lamina is better defined. Externally elastin fibrils are formed. Some of the spiral arteries may actually, on reaching the surface epithelium, continue in a course parallel to the surface. There is an increase and thickening of the venous stems and collagen and elastin can be demonstrated in their outer coat.

During the early secretory phase, the spiral arteries increase in length. Their terminal branches are coiled and their lower parts are even more so. The media has now become impregnated with elastin fibrils. The veins are even more distended than the arteries. The

larger venous stems dominate the picture. There is reduction of the glandular plexus and a number of sinus-like expansions may be found. The height of the endometrium has been considerably augmented and the stroma is oedematous at this stage. The phosphatase distribution in the surface and glandular epithelium remains unchanged during this phase.

In the late secretory phase, the stromal oedema is even more extensive. The coiling of the arteries decreases and they undergo degenerative changes. The intima and adventitia of the arteries are weak. The media contains only a few elastin tissue and have the appearance of being subject to a diffuse pre-hyalinisation. Some of the capillary endothelial cells appear to be swollen and exudation of fibrin is observed around the veins and capillary tubes. Infiltrations by numerous leucocytes and plenty of blood-extravasates are in evidence everywhere in the superficial layers. The venous lakes are still further developed and the venous stems are coiled in appearance. The walls of these stems are comparatively thick. Towards the end of the late secretory phase they begin to shrink. It has to be noted that by the late secretory phase there is a sharp reduction in the phosphatase content of both surface and glandular epithelium. It has also to be noted that from studies with mice uteri it has been found that the phosphatase in the endometrium is under control of steroid sex hormones (5). Atkinson and Engle (6) have stated that in the human female this enzyme system may play an active part in such hormone-regulated processes as endometrial growth and fat and glycogen metabolism. The assertion that alkaline phosphatase is associated with glycogen metabolism is denied by Hertig, and Gomori states that the relationship is not a strict one. Corner on the other hand, associates it with phospholipid and not with carbohydrate metabolism.

During menstruation in the desquamated parts of the endometrium the spiral arteries jut out from the lacerated surface but remain closed by a small clot. In the non-desquamative regions the arteries are less coiled. During menstruation the capillaries show extreme distension in the entire superficial region as well as in the adjacent parts of the spongy layer. Analogous features are exhibited by the venous plexus. Menstruation serves as a link in a chain of events necessary for reproduction and it permits of subsequent ovulation. The cause of menstruation according to Allen (8) is estrogen deprivation but this theory does not account for abnormal menstrual bleeding. Menstruation starts in the human female at about the age of twelve to fourteen years with a range of nine to eighteen years. Menstruation lasts for one to seven days; in over 90% of females it lasts from three to six days. The weight of the discharge is from 20 - 500gms.

Macht reported that circulatory blood, sweat and saliva at the time of menstruation contained a substance toxictoplant growth (9, 10). Smith and Smith demonstrated that menstrual blood contains a toxin which is derived from the secretory endometrium and is closely related with an atypical euglobulin (11). The toxin is similar to necrosin, which is obtained from pleural effusion in animals from irritation due to local turpentine infections (12, 13). It is produced possibly by a defective progesterone secretion and by other unknown factors. The toxin is believed to stimulate the pituitary, causing release of gonadotrophins and adrenotrophins. Un-extracted mentrual blood is lethal when injected into immature male rats. Fibrinolysin is found in pseudo-globulin fraction of menstrual discharge. The protective pseudo-globulin is present at catamenia to neutralise the menstrual toxin. It has been isolated from pleural and ascitic fluid of cancer patients. George Van S. Smith postulates that all the symptoms and signs associated with menstruation are due to activity of the menstrual toxin with possible exception of soreness and engorgement of breasts. According to the same authority the amount and duration of menstruation depends on the amount and rate of formation of the toxin and whether it is formed locally or diffusely (14). What mechanism is behind menstruation is a question which many have asked and only incompletely answered. Schlegel and Dalgard have found A-V passages in the human endometrium, an assertion denied by Bartelemez. Schlegel's theory of menstruation hinges mainly on the existence of these A - V anastomoses. Menstruation is preceeded by a sudden anaemic condition of the superficial endometrial tissue and this, according to Schlegel's theory may be ascribed to the opening of the numerous A - V channels at the pre-menstrual stage. Such an opening is said to be due to a substance of the Ach group. It has to be noted that in between the functional and basal parts of the endometrium are found nerves along the intensely-coiled first parts of the spiral arteries. In the endometrium the nerves are of the Ramak type. A periarterial nerve plexus has been found to extend from the myometrium and follow the spiral arteries for a distance up in the functional layer. When Ach conc. in the endometrium is high enough, it is postulated that the A - V channels open and result in a decreased blood flow combined with congestion peripherally. See figure back page. Markee (15) claims that the spiral arteries are not permanently differentiated from the straight ones and a certain amount of inter-conversion occurs. Before the onset of menstruation the spiral

arteries do not shorten while the endometrium is decreasing in thickness. The spiral arteries however at this time become much twisted and buckled. Markee has found that there is a time relation between the merosis of the endometrium and the stasis in the spiral arteries. It has also been found by Bartelemez (16, 17) that it is contraction in the spiral arteries found in the basalis or at the junction between the basalis and the myometrium that controls the amount of blood lost at menstruation. Markee attributes the cause of menstruation to the decrease in number of capillaries supplying blood to the stroma, to the decreased rate of flow in the capillaries and to the decrease in pressure in endometrial capillaries brought about by a fall in the blood level of estrogen and progresterone.

Cervix: Under the influence of estrogen the epithelium of the cervix tends to revert to the stratified squamous type and the glandular secretion increases and becomes highly alkaline. The mucus when dried on a clean slide crystallises in a fern-like pattern and can be stretched into threads. During the progesterone phase of the menstrual cycle the cervical mucus is less alkaline, more scanty and viscid in character. It also loses its fern-like pattern and the property of being easily stretched into threads.

Vagina: Vaginal smears present a characteristic appearance according to when the smear was obtained. If a post-menstrual smear is obtained and suitably stained, many cyanophilic cells with vesicular nuclei can be seen. The proportion of cells showing eosinophilic staining is high. The percentage of superficial cells with pyknotic nuclei is also high (karyopyknotic index). In three or four days before ovulation the percentage of large eosinophilic cells increases and this is followed by a rise in the karyopyknotic index. A smear taken just before ovulation shows squamous cells already separated from each other and most of the cells have a pyknotic nucleus. A post-ovulatory smear shows a decrease in the eosinophilic and karyopyknotic indices. The cells appear in clusters and show some curling. As the luteal phase approaches the cells become more cyanophilic and folded. The nuclei are nearly all pyknotic. Degenerative changes in cells can be seen and so the smear looks "dirty".

Fallopian Tube: During the proliferative phase there is a uniform growth of the columnar cells and the rate and amplitude of the peristaltic contractions gradually increase. During the secretory phase the tall columnar cells regress and the non-ciliated cells begin to secrete and their height becomes greater than those of the degenerating columnar cells. The rate and amplitude of the peristaltic waves gradually decrease.

Breast: Breast changes are dependent on the cyclic hormonal secretions of estrogen, which is chiefly responsible for the development of the ducts and progesterone which is chiefly responsible for the growth of the lobular alveoli. In the mid-period stage the ducts expand to form new ductules and the acini enlarge. During menstruation there is a round-cell infiltration of stroma, and regression of proliferating epithelial ducts. In the post-menstrual phase the stroma is compact and the round cells disappear and the acini are small.

Ovary: As all these changes in the breast, uterus, vagina etc. are taking place the ovary is also undergoing very important developmental changes. F.S.H. does not only cause follicular development but causes also the ovary to secrete estrogen. The estrogen affects the reproductive tract in a manner outlined above and the estrogen level reaches its highest after two weeks of secretion. By then its blood concentration is great enough to stimulate the pituitary to secrete L.H. This last hormone causes ovulation and is responsible for the corpus-luteum formation. The mechanism of ovulation is still unknown. Some workers claim that it is due to an increase in intrafollicular pressure, while others vouch enzyme theories for it. Neither of these theories can on its own merits account for ovulation. For example, it has been found that in fish, amphibia and certain mammals there is no accumulation of antral fluid and so the intra-follicular pressure mechanism in these cases obviously cannot operate. As to the enzyme theory it is very difficult to explain how the various enzymes cause a break in the follicular wall in a relatively small and circumscribed are comprising the stigma. Ovulation appears to be due to morphologic changes in the follicular wall brought about by gonadotrophic and other hormones. It has been found thanks to the splendid work of many research workers in this field, that in a majority of females with a menstrual cycle of length between twenty-four to thirty-four days, ovulation takes place between the tenth and the fourteenth day from the onset of menstruation. In a minority ovulation takes place between the eight and the seventeenth day after bleeding starts. Ovulation timing is a procedure of the greatest importance. It can be timed by plotting basal body temperature-curves for the whole length of the cycle. Ovulation is marked by a fall followed by an immediate rise in temperature. Other methods (18) for timing ovulation include the examination of vaginal smears, Lanis-rat ovary hyperemia test, fern test, Birnberg glucose-stick, fertility testor of Doyle and Ewers and pregnanediol essay. The explanation of each of these tests is quite beyond the scope of this article. Ovulation having

taken place, the corpus luteum which is then formed secretes progesterone for about two weeks.

The purpose of the menstrual cycle is to cause ovulation and at the same time ovulation must take place for the cycle to be normal. Still there is much to be known on this subject but, as has been seen, much progress has been made since the days when it was thought that the cycle was under the control of the moon.

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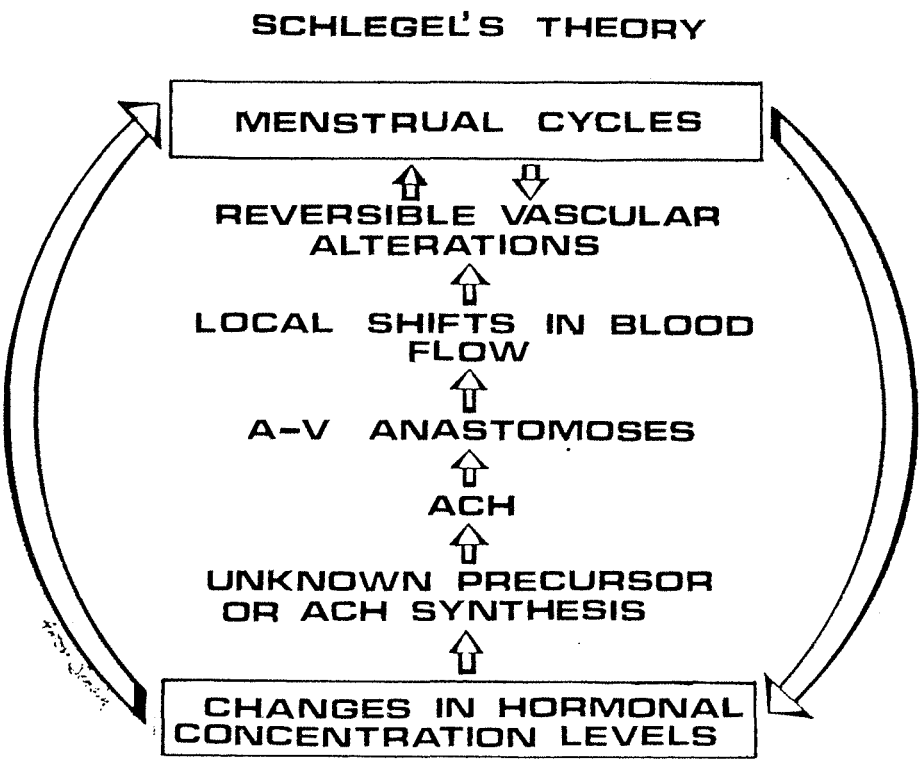

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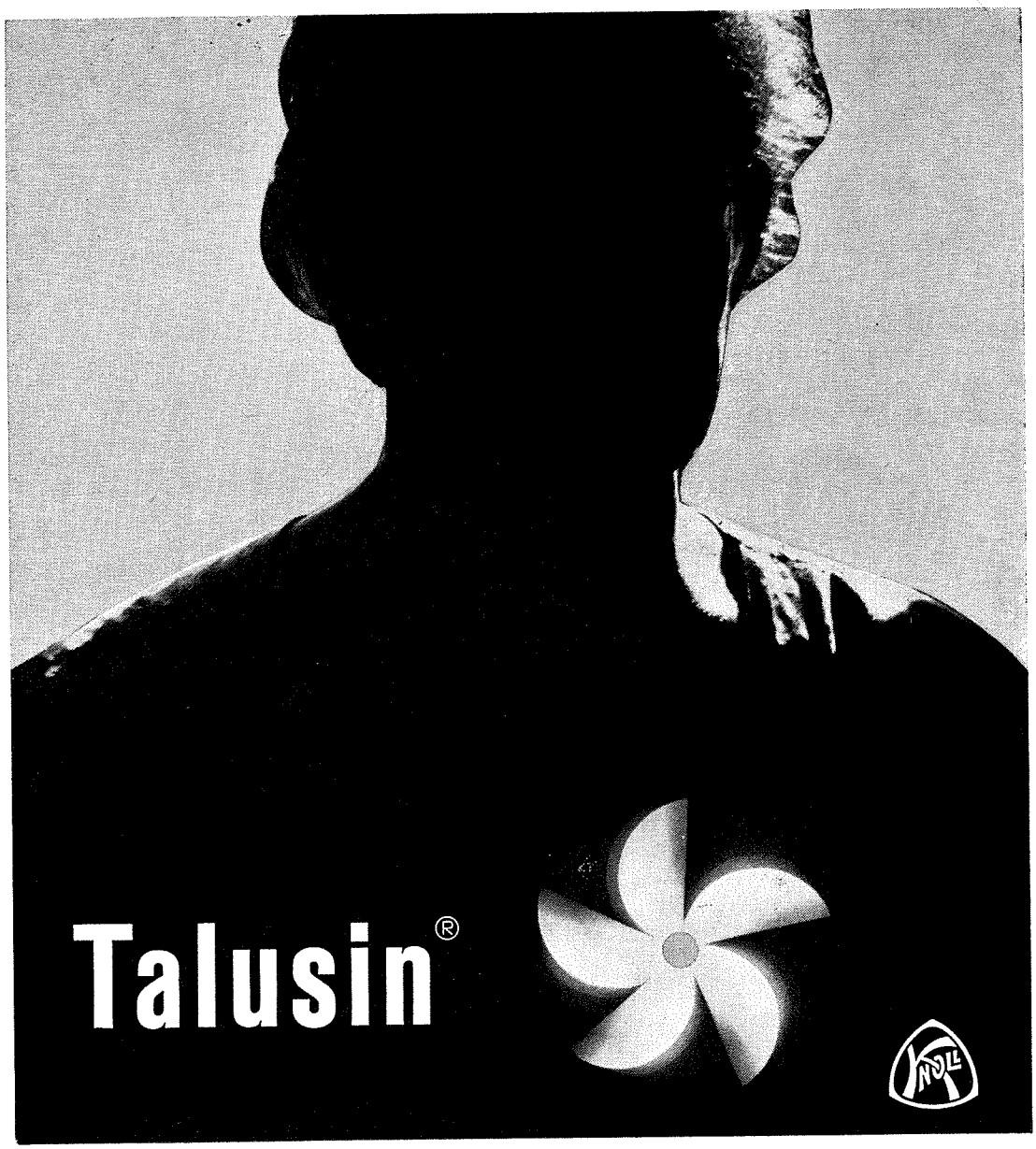

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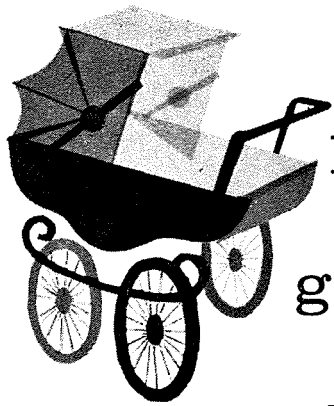

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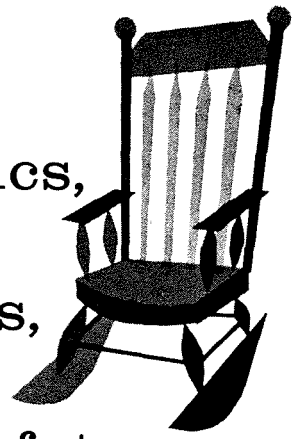

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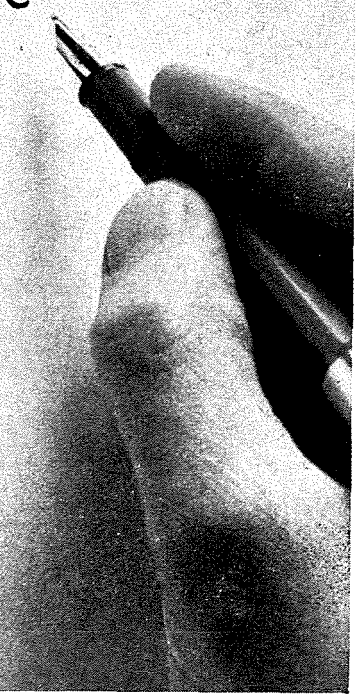

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