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PUBLIC HEALTH IN MALTA

From time to time it is proper to examine a situation and to assess the success or failure of any activity. The health of the people of Malta is one aspect of life in which this is useful and indeed necessary. As it happens we find that the extent to which we have succeeded in improving matters is strong enough to provide the incentive for yet stronger endeavours. In 1966 there was no case of trachoma — that bane of the twenties —, we find a single case of puerperal sepsis, there were only 23 cases and no deaths attributable to our old enemy Brucellosis. This latter is a victory which must some time be described in detail, although in this, as in so many other cases where bacteria are concerned, safety is guaranteed only on condition of unceasing vigilance. In any case, it should be recorded that this figure for Brucellosis is much smaller than it has ever been. We must be thankful there was only one case of poliomyelitis and one case of cerebrospinal fever. Infantile mortality which had always been high, reached the record figure of 345 per 1,000 births in the tragic year of 1942 but has decreased at least tenfold. This again is a heartening success due to therapeutic and hygienic advances, and altogether, though one is naturally on guard against

such complacency as might traditionally irritate some watchful Fate into retributive action, in this sceptical age we venture as far as giving not the mean, though fashionable, "two cheers" but the full three lusty ones for such progress as has been achieved. The fortunate young people of today, living an artificial life in cities, drinking safe water, sufficiently fed, breathing unpolluted air find it hard to imagine different conditions.

Still when the cheering has died down, we find many reasons why we should not rest on our laurels. In 1966 we had an epidemic of whooping cough, with 337 reported cases, one of chicken pox with 322 cases, 71 cases of pulmonary tuberculosis, 29 cases of other form of tuberculosis, 23 cases of measles, 6 cases of diphtheria, 19 cases of typhoid and 6 deaths from tetanus. The continued limited existence of leprosy is a persistent challenge to our profession. Caused by a bacterium still practically not cultivable, transmitted by means which are mostly conjectural, this illness still defies us.

It seems to us the time has come to revise some, at least, of our health legislation. The Medical and Health department wisely spends a great deal of time, energy and money in persuading the public to accept vaccination against diphtheria, whooping cough, tetanus, tuberculosis and poliomyelitis. These things are done and go on being done in the schools, in clinics, mobile or fixed, and in various ways to an extent which is not known by and would probably surprise the ordinary medical man. We are glad to find the Health department is bold and *avant garde* enough to use B.C.G. as a prophylactic against leprosy, but it is strangely true that the only illness against which vaccination is still legally compulsory is the exotic and uncommon smallpox. This is probably still a good thing (though the age at which it is done could bear reconsidering) but why should compulsion not be extended to all the diseases which it is possible to prevent specifically? We hear of a highly disturbing proportion of refusals by parents to allow even such a thing as B.C.G. vaccination. Why should a society which rightly

condemns a parent who, being a member of some reactionary sect, would stop his child from receiving a life-saving blood transfusion allow other parents to deprive a child of a protection which also could be life-saving? And why, to put it at its lowest, should health departments have to fritter so much of their energy in persuasion when a legal enactment might put order where there is now a fair amount of confusion, put completeness where there are now so many deficiencies? We are positive that, given a certain preliminary amount of explanation, the present-day public would welcome such enactments and no government which has the courage and sense to push such proposals through would lose popularity more than momentarily.

Apart from the infectious diseases the general health of the community is good. Here, as elsewhere, we have the problem of lung cancer perhaps to some slightly less degree than elsewhere, smoking being rather less common with us (and very notably so, as far as women are concerned) than elsewhere. Here also there is an onus on the public health authorities to publicise the dangers of smoking and to do all in their power to stop it. It would be interesting to see whether we could succeed where far greater countries have failed.

One is not so sure how far the mental well-being of the people matches its physical health. These are things difficult to assess. We have the impression that ignorance and stupidity are far commoner than they should be. While almost every single individual seems to possess a sort of animal cunning which serves him to secure his own survival and to do his share in the survival of his species, egotism, crudity and bad manners are so common as to constitute a veritable epidemic of what one can only charitably consider as a disease. The time may come when such things are studied and treated as medical problems, but there will be no short cuts to success and no vaccine to remedy matters. It is a great pity that there are things in this world beyond the powers of microbiologists to deal with.

HUNTINGTON'S CHOREA, WITH SPECIAL REFERENCE TO ITS INCIDENCE IN MALTA

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The epidemiology of mental disorder is at the moment assuming a role of increasing importance. This aspect of psychiatry, however, still awaits study in Malta. It was, therefore, considered that a review of my experience of the morbidity and prevalence of such a disabling disease as Huntington's Chorea in Malta over the past twenty years might be of interest.

Huntington's Chorea is known to be a hereditary degenerative disease of the basal ganglia and of the cortex of the brain. It commonly manifests itself clinically at middle age in the form of choreiform movements or of muscular rigidity, which are often accompanied by mental deterioration.

The case material on which this study is based was either seen personally, the observations being complemented by information obtained from normal relatives of affected individuals, or else gathered from past records at the Attard Mental Hospital since 1861 and at the St. Vincent De Paule Hospital since 1892. The records from these two hospitals were found useful in tracing present cases back to their ancestors and in constructing family pedigrees but were otherwise of limited value for two reasons: (a) they were indicative only of a part of the prevalence of the disease since only the more severe mental cases found their way into hospital; and (b) the entries of the older records are not so detailed and exhaustive as to satisfy the clinical research worker though they may have served their purpose for the routine hospital work of the time.

I have been able to collect 22 Huntington's Chorea families in Malta com-

prising 125 cases. Of these 72 were men and 53 women; 100 are dead and 25 alive. The number of cases personally observed is 26. This number has been limited by two factors: (a) Huntington's Chorea is an uncommon disease and, therefore, no large series of cases may be expected to be found in a small population as that of the Maltese Islands (317,739 in May 1966); and (b) there are no means, such as notification whereby all existing cases can be traced and examined. It is, therefore, realized that the statistical data of the present study though approximate are not final and are likely to be an underestimate of the actual prevalence of the disease amongst us.

Historical

A form of chorea called St. Vitus's Dance or Dancing Mania occurred in Europe from the tenth century onwards. The malady sometimes took epidemic proportions in the Middle Ages and was characterised by gesticulations and excitement. The reference to St. Vitus is due to the fact that patients suffering from the disease went processionally in search of a cure to the chapel dedicated to this saint in Zabern (Alsace) in 1418 (1). In Italy it was ascribed to the bite of a venomous spider, the tarantula, and was therefore called tarantism. In later years the disease was considered to be of an hysterical nature (2). It is not possible to say what is the relationship of St. Vitus's Dance and tarantism to the conditions which we today identify as Huntington's Chorea. This form of chorea was first described in the U.S.A., the earliest report of a case going

back to 1816. Other descriptions followed in 1834, 1841, 1848 and 1863, the disease being variously referred to as Chorea Major, Pandemic Chorea, Hereditary Chorea, Chronic Hereditary Chorea and Chronic Chorea.

The most detailed and comprehensive description of the disease was that of George Sumner Huntington (1850-1916) who read a paper "On Chorea" before a medical society on the 15th February 1872. This American physician had the opportunity of studying cases observed since 1797 by his grandfather and by his father (Abel and George respectively) in one of the American foci of the disease in Long Island (3). He emphasised the hereditary character of the disease, its appearance in adult life and the tendency of affected persons to become psychotic.

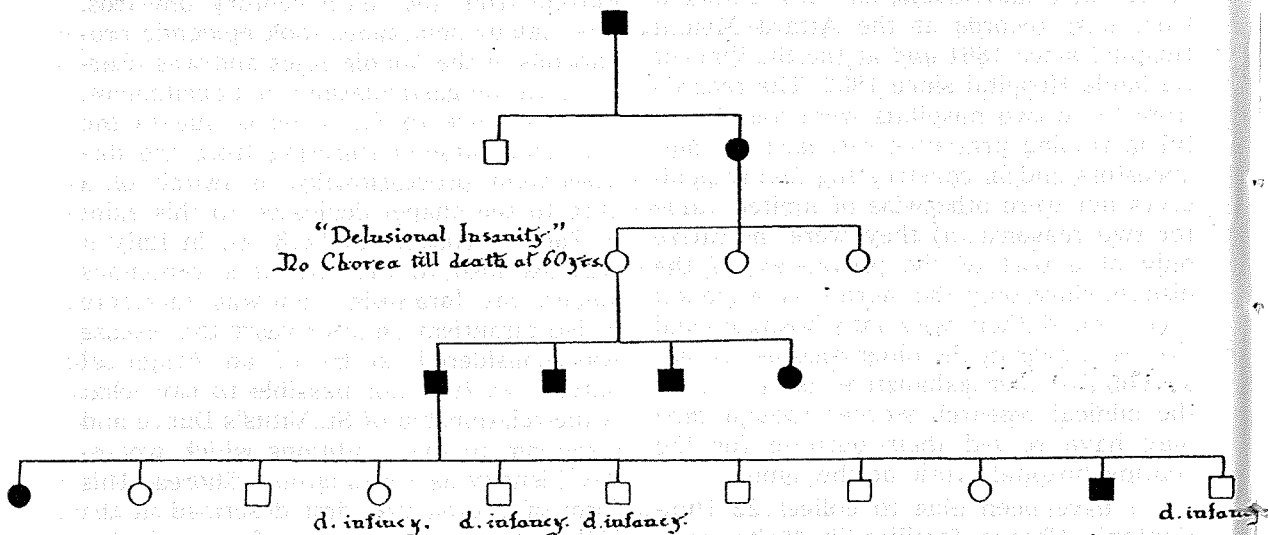
It has been established that the cases observed in the U.S.A. were descended from two brothers who emigrated from Bures in Essex, England, to Boston Bay in 1630. Sufferers from the disease were tried for witchcraft in the Colonial Courts of America and others were persecuted as it was traditionally believed that a remote ancestor of the affected families was cursed with the disease because he had

mocked Christ on the Cross (4). During the succeeding three centuries about one thousand descendants of the original pair have suffered from the disease up to 1932 (5).

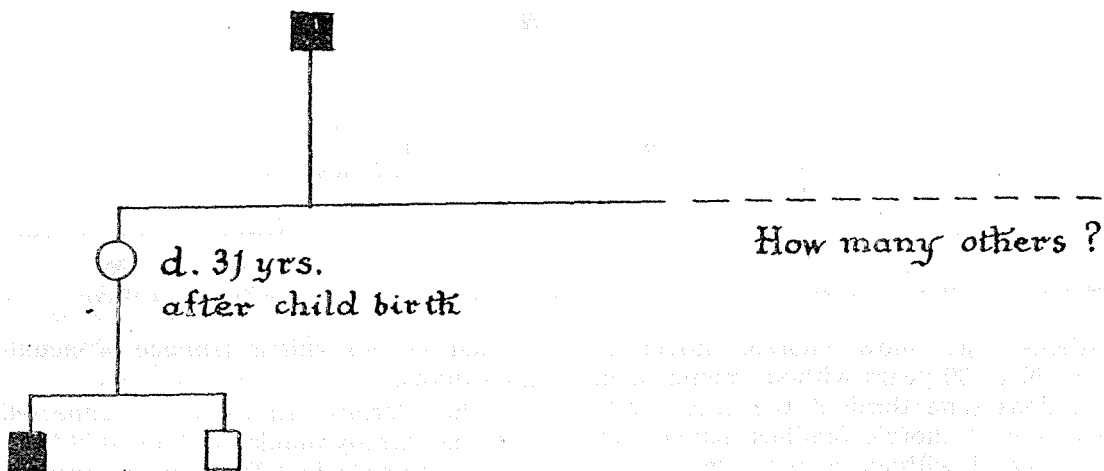
Since 1872 the disease has been reported from different parts of the world. In Britain the first case was recorded in 1887 (6). In Malta the earliest documented instance of Huntington's Chorea that I have been able to trace dates from January 1872. The patient was a man of 70 years from Żurrieq who was admitted to the Ospizio at Floriana and diagnosed as suffering from St. Vitus's Dance. It is of interest to note that some of the early cases seen in the late 19th century in Australia (Victoria) were similarly labelled (7). There is no doubt that the Malta case diagnosed as St. Vitus's Dance was one of Huntington's Chorea for I have succeeded in tracing the subsequent history of his pedigree up to the present day (*Ped. 1*). Needless to say this patient could not have been labelled as Huntington's Chorea in January 1872 because, as already stated, it was exactly in February of that year, that is a month later, that George Sumner Huntington read his paper on this malady in America.

**Oldest known family with Huntington's Chorea
1872—1966**

Pedigree I



Pedigree II



A further case to be diagnosed in Malta, this time as Chronic Chorea, was a woman of 64 years from Mosta who was admitted to the Mental Hospital in 1888. The first patient to be labelled as Huntington's Chorea was a man from Hal Għarġur who was admitted to the same hospital in May 1916.

Heredity

Huntington's Chorea affects both sexes. It is transmitted as a single autosomal dominant gene directly to the children from either parent. Instances of three monozygotic twins have been recorded where both of each pair developed the illness (8). Theoretically one expects 50% of

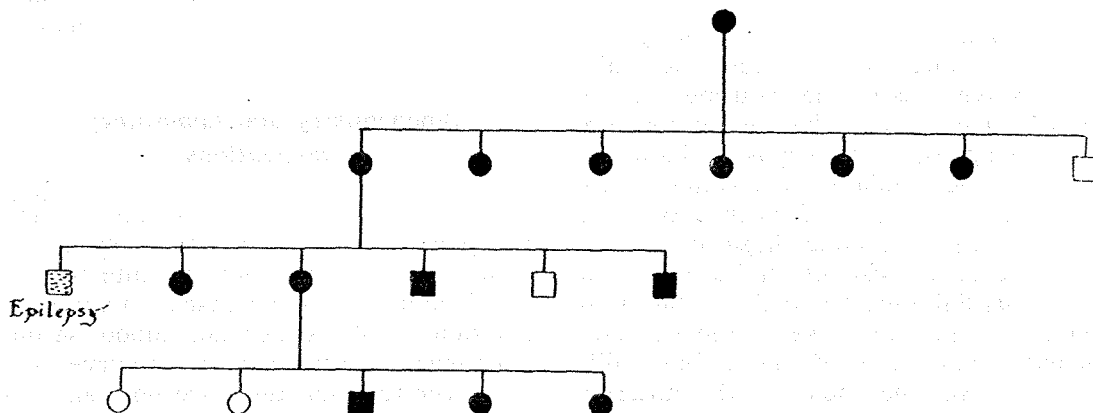
the offspring to develop the disease but in actual practice the incidence is in the region of 30% although instances of higher percentage are met with (9) (See Peds. 1 and 4).

It has been said that Huntington's Chorea never skips a generation (10) but instances have been described, though infrequently, where the disease does not appear in one or two generations but manifests itself in a later one (11) (See Peds. 1, 2 and 3).

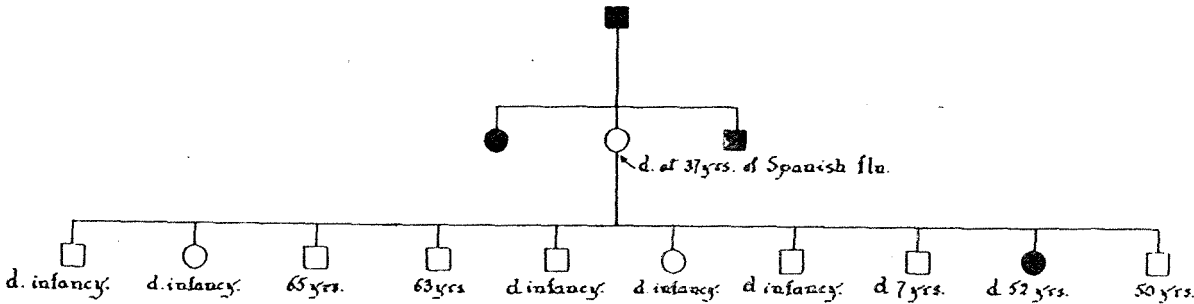
Members of the affected families who escape the disease do not transmit it to their offspring (12).

It seems that the mental and motor traits are inherited separately and more or less independently of one another. Thus

Pedigree IV



Pedigree III



patients may show choreic movements from 20 to 30 years without mental manifestations (one third of the cases) while members of choreic families may become mentally ill without motor signs, the so-called cases of "Huntington's Chorea without chorea" (13).

Sometimes there is a negative family history. In such a case the appearance of the disease is due to a spontaneous new mutation in a germ cell of one or other normal parent (14). This is a very rare occurrence, the estimated rate of mutation for Huntington's Chorea being 5 per million per generation. However, the appearance of a case with a negative family history may also be an instance of a "skip" where the disease does not appear in previous generations which, therefore, appear normal; or else the patient may be an illegitimate offspring whose real father is not the normal one shown in the pedigree but another one suffering from chorea.

Pathology

Although the lesions of Huntington's Chorea are diffused throughout the brain, they involve mostly the neurones of the frontal cortex and of the corpus striatum (basal ganglia). The corpus striatum is formed of the Caudate Nucleus and of the Lentiform Nucleus. The former is made up of small cells resembling those of the cortex; the latter consists of the Putamen and the Globus Pallidus. The cells of the Putamen are small like those of the Caudate Nucleus, while those of the Globus Pallidus are large like those of the anterior horns of the spinal column. They are

marked by two whitish laminae of medullated fibres.

The Corpus Striatum is connected with the extrapyramidal system (Red Nucleus and Rubrospinal Tract) which terminates round the motor cells of the anterior horns of the spinal cord from which rises the motor fibres to the muscles. The extrapyramidal system exercises a coordinating and inhibitory control over the motor cells and fibres just mentioned.

The lesion of Huntington's Chorea consists of a degeneration and atrophy of the small cells of the Caudate Nucleus and Putamen (which are really one nucleus) and of the neurones of the cortex of the brain especially of the frontal region. As a result there is a general shrinking of the brain (white and grey matter) and secondary dilatation of the internal ventricles and hydrocephalus. These lesions give rise to the hyperkinetic and hypotonic form of the disease. When, in addition to the damage of the above-named structures, there is also loss of the large cells of the Globus Pallidus, the disease assumes the akinetic and Parkinsonian or rigid form (15).

Biochemistry and Laboratory Investigations

Brain: the only consistent finding is copper reduction in all parts of the brain, except in the central white matter and thalamus, and increased amounts of strontium. CSF is normal. Blood serum copper levels are normal, sugar curve normal. Liver function tests are normal. Urinary copper excretion is normal. Other

routine laboratory investigations are normal. EEG is normal or may show evidence of cortical degeneration but no specific changes (16).

Aetiology

It is not known what produces the degenerative changes of Huntington's Chorea but it is thought that they are due to some inherited metabolic defect as has been shown, for instance, to be the case in Wilson's Hepato-Lenticular Degeneration which appears to be due to an abnormal copper metabolism and is characterised by the deposition of excessive amounts of copper in the brain and liver and by increased excretion of copper and aminoacids in the urine (17).

Age of onset

The majority of cases begin between the ages of 30 and 50 the average being about 42 years. The onset is slightly earlier in women than in men. However, variations, both individual and familial, occur in the age of onset. In fact cases have been recorded with an onset ranging from such extremes as 3 to 60 and even 70 years of age.

The clinical picture tends to vary with the age of onset. In cases starting in the twenties or earlier, rigidity and slowness are the main signs; in the forties choreic movements are the characteristic

features; and in the sixties, intention tremor is the chief manifestation (18).

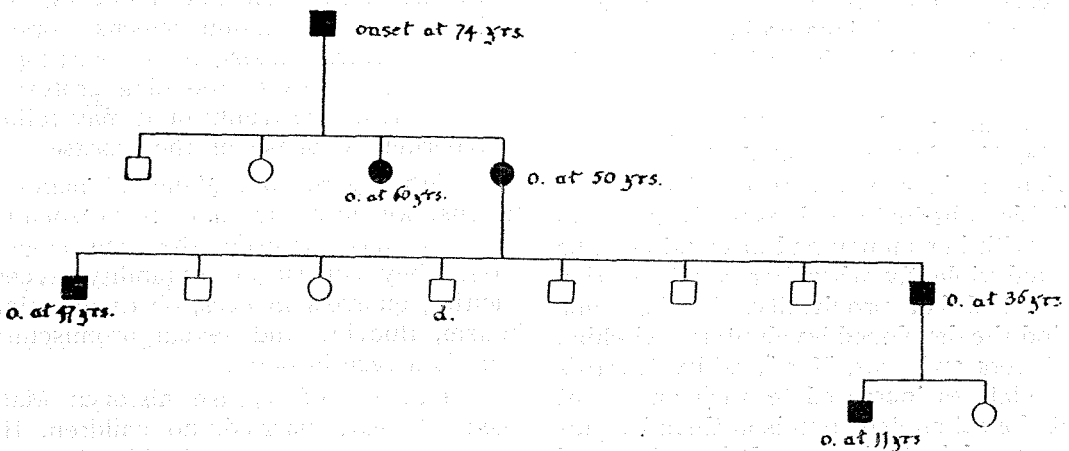
According to some investigators the disease tends to appear at earlier ages in succeeding generations (19) but other workers do not uphold this so-called Anticipation Theory (20). I have, however, come across a few cases in Malta which lend support to it. (Ped. 5).

Clinical Picture

The clinical picture is the result of the combined pathological involvement of the basal ganglia and cortex. It, therefore, consists of neurological and mental manifestations with or without the presence of some other associated disease. The features presented by our cases are identical with the descriptions given by other authors who studied the disease abroad. The neurological changes are either of the hyperkinetic and hypnotic type or of the akinetic and rigid type. This akinetic form may be found by itself or superimposed on the hyperkinetic type or following it. The mental changes consist of personality alterations, psychoses or dementia. The associated diseases are usually mental deficiency and epilepsy.

The neurological signs usually appear before the mental ones but there are instances in which the psychic disturbances precede the neurological changes by many years; or else the neurological and psychotic manifestations appear simultaneously.

Pedigree V



The hyperkinetic type of the disease begins insidiously with involuntary movements of a jerky and irregular character. They are abrupt and coarse. They may start in any part of the body but the face, neck and upper limbs are usually the first to be affected. In the face they take the form of grimacing, twitchings of the corners of the mouth, pursing of the lips and raising of the eyebrows. Speech is indistinct and explosive with grunting noises. There is difficulty in swallowing, with choking during meals.

In the upper limbs the movements consist in fiddling and clumsiness of the fingers which progress to abrupt extension-flexion movements of the digits and wrists causing the patient to drop objects from his hands and rendering him unable to dress himself and do housework. In the end he may be so incapacitated that he has to be fed, dressed and attended to with regard to his personal hygiene and other needs.

Owing to the involvement of the lower limbs the gait is unsteady, curtsyng and staggering, the patient walking on a wide base to offset his ataxia. The movement may ultimately become so severe that he falls to the ground and has to be nursed in bed.

The choreic movements are increased on voluntary effort but disappear during sleep. Apart from these disturbances there may also be twisting and athetoid movements of the limbs and trunk.

On neurological examination we find increased deep muscle reflexes, decreased muscle tone and inco-ordination (finger-nose test, etc). The plantars remain flexors.

Summary of a case history: Female, single. She first manifested abnormal behaviour at the age of 39 years. She became irritable, obstinate and excessively generous with her money and possessions. She reacted violently when her relatives tried to control her prodigality. At the same period she developed involuntary twitching of fingers and toes. Her hostility towards her relatives increased to such an extent that she attempted to poison them by putting cresol in their soup. When thwarted

in her desires she threatened to commit suicide. By the age of 41 years she had become very erotic, claimed to be engaged to a high ranking personage, exposed herself at home and appeared indecently dressed in public. The choreic movements became more pronounced involving the head, trunk and all four limbs. Her gait became so unsteady that she sometimes lost her balance and fell to the ground. Owing to the ataxia she had to be confined to bed during the last two years before her death.

The akinetic and rigid variety occurs at an earlier age — some thirteen or fourteen years — than the typical choreic form but is much less frequent (21). There is rigidity and stiffness of the body, a bending forward of the trunk, adduction or slight abduction of the arms and flexion of the elbows, wrist and finger joints. The facies is expressionless and immobile with staring eyes and infrequent blinking of the eyelids; the speech is slurred and drawling. The patient moves slowly and walks in small quick steps but running is easier than walking. On neurological examination there is cog-wheel rigidity on passive movements of the elbow; poor co-ordination and increased deep reflexes with ankle clonus and extensor plantar reflexes if the pyramidal system is involved (22).

The akinetic and rigid variety may occur by itself; or it may be superimposed on the hyperkinetic form when the choreic movements may change into athetosis (slow twisting movements of fingers, face and tongue) and torsion spasms (torsion dystonia) which consist in the twisting of the spine and pelvis producing grotesque contortions of the trunk; or it may follow a hyperkinetic phase of the disease (23).

With regard to the mental manifestations, we may find that the personality changes may precede the neurological ones. They consist of irritability, eccentricities, quarrelsomeness, obstinacy, alcoholism, thieving and sexual promiscuity. Here is a case in point.

Summary of a case history: Male, aged 40 year, married, no children. His wife observed a change in his character

at the age of 37 years. Previously docile and efficient at his job, he started complaining of a feeling of being unsettled, of tiredness and insomnia. He became progressively irritable, stubborn, quarrelsome and aggressive, swearing on the least provocation and inclined to drink excessively. Because of his hostile tendencies he has come in contact with the police on a few occasions and has been sent away from at least two jobs so that he remains unemployed to the present day.

At times he feels mildly depressed for short periods. Occasionally he is seized by intense fear, almost amounting to panic, or by a feeling of being on the verge of losing consciousness. Since about six months his fingers "keep moving against his will". He tries to control them by flexing them in his palm as if forming a fist. His grip on objects is so unsustained on account of these movements that he spills liquids from glasses held in his hand. There are also sharp "kicking" jerks in his legs.

His mother had chorea; two brothers also suffer from the same condition. He was first seen six months ago when he was placed on phenothiazines. He is now less irritable, is sleeping well and his movements are less frequent and pronounced but his behaviour remains unchanged.

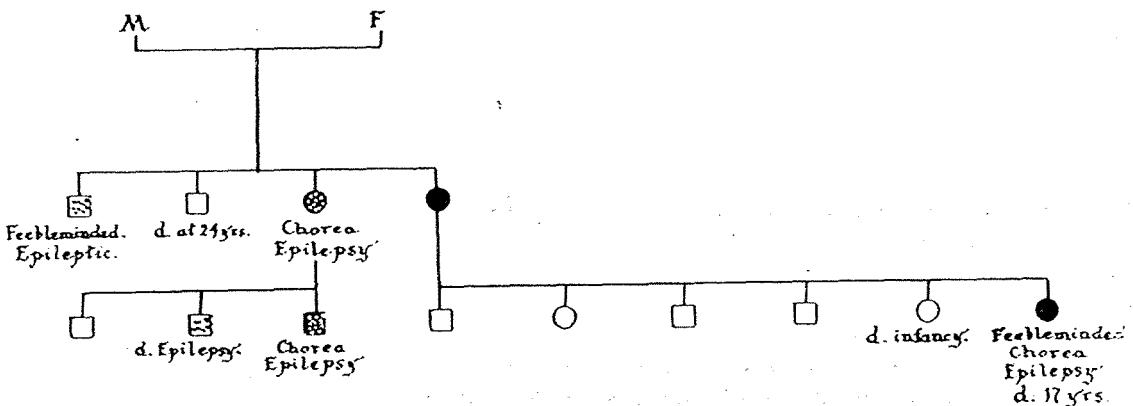
The psychoses may occur before the appearance of the chorea or may arise during its course. They take the form of mood disorders, ranging from apathy to depression with suicide or mania; para-

noid or schizophrenic reactions; and confusional states (24).

The dementia may have a delayed onset or may never appear in some cases. When it occurs it is progressive and consists in the usual features of defects of memory, impaired judgment, disorientation, emotional lability, restlessness and self-neglect (25).

The following case-history illustrates these features. Female, aged 61 years, widow, no children. Onset of her illness dates since three-and-a-half years ago with involuntary movements of the limbs which have grown steadily worse. Concurrently with the developments of these limb movements, her relatives noticed that she started to become neglectful of her personal appearance and of her home. She often stayed naked at home. When she went out she was a cause of embarrassment to motor-drivers because of her unsteady gait. On one occasion she was hit by a motor-bike but suffered no serious injury. She has become obstinate, ignoring advice and refusing the help of others. She has been telling people that she wants to get married again and actually came across a paralytic who accepted to marry her if she gave him £100. She is forgetful; for instance she would go to the grocer but would not recall what she went there for; or would forget to pay for goods or else would go to a flower-shop and ask to buy a stove. Though she is oriented to place, she is only partly so to time and

Pedigree VI



person. She has no insight into her condition.

Mental deficiency and epilepsy may be found not only in patients affected with chorea but also in other non-choreic members of the family (*Ped.* 6). The genetic relationship of these associated diseases with Huntington's Chorea is not clear ⁽²⁶⁾.

Duration of the disease

The average duration of the disease is 11 to 16 years for both the choreic and the rigid/akinetetic forms, the shortest duration on record being two years from the appearance of symptoms and the longest 50 years ⁽²⁷⁾. The illness persists until the patient dies but there may be periods when it becomes stationary ⁽²⁸⁾.

Death is from exhaustion or inter-current disease ⁽²⁹⁾ or choking while eating. These patients have a voracious appetite and they tend to gulp their food; hence the importance of giving them nourishment in a semi-solid form to avoid choking.

Differential Diagnosis

Huntington's chorea must be distinguished from other conditions manifesting choreic movements or rigidity. The main conditions that must be considered in the differential diagnosis are:

1. Sydenham's chorea which is associated with infectious diseases (such as puerperal and rheumatic fevers) and carditis. The family history is negative.

2. Hemichorea due to embolic brain disease.

3. Post-encephalitic parkinsonism. Here one may encounter serious difficulties as, apart from the rigidity, choreiform and athetoid movements may be found in parkinsonism. A past history of an acute feverish illness with headache and lethargy points to post-encephalitic parkinsonism. There is an absence of a family history of Huntington's chorea.

4. Senile chorea. This is not hereditary and is not necessarily accompanied by dementia.

5. Psychoses. When Huntington's chorea starts with a psychosis such as depression, paranoid state or dementia,

the only feature that clinches the diagnosis, until the appearance of choreiform movements, is the family history.

Prevalence

Reliable statistics of the prevalence of Huntington's Chorea are not available. Estimates vary widely from about 4 cases per 100,000 population in Michigan, U.S.A.; 5.5 in the Duchy of Cornwall and 7.2 in the county of Northamptonshire, England ⁽³⁰⁾.

Basing ourselves on the number of living cases of Huntington's chorea known to us ⁽²⁵⁾, the prevalence in Malta (population 317,739 in May 1966) works out at 7.8 per 100,000; but the actual figure is likely to be higher than this for the reasons already stated at the beginning of this paper. The number of cases is likely to rise as more patients will come to light with a heightened awareness of the disease among medical practitioners. The emigration of thousands of healthy individuals each year will also lead to an apparent increase in the prevalence of the disease as the affected members are left behind in Malta. Apart from these two factors, we may expect a real increase in the number of persons at risk owing to the diminished infantile mortality rate as more gene-carrying babies are destined to survive and reach adult age to develop the disease and transmit it to their offspring.

Distribution of the Disease in Malta

The main focus of the disease is Hal Għargħur with six families; then follow Sliema with five and Qormi with three families. Naxxar, Mosta, Valetta and Senglea have two families each. Żebbuġ, Floriana, Marsa, Tarxien, Balzan, Luqa, Mqabba and Gżira possess one family each. These foci are in no way fixed for affected members of one family sometimes move to another town or village thus giving rise to a new focus in a different place. For example the descendants of the first case known to us have moved from Żurrieq to Valetta, Floriana and Marsa. The

least mobile have been the cases from Hal Gharghur perhaps because, being agriculturalists, they were tied down to the soil and because their village remained somewhat isolated from the rest of the Island until quite recent times owing to the lack of adequate transport in the past. On account of these factors Hal Gharghur remained a relatively closed community and this explains why this locality shows the biggest concentration of families. It must, however, be admitted that it has not yet been possible to find a common origin for the various affected families in this village. This may be due to the fact that owing to inadequate and incomplete information about their ancestry, the pedigrees cannot be traced as far back as the generation where linkage by marriage may have initially started.

No cases have so far been met with from Gozo.

Although there is one particular surname that occurs more frequently than any other among patients with Huntington's Chorea I have counted forty-seven other surnames of individuals that have suffered or are suffering from the disease. Five of these surnames are British but in only one instance is there the possibility that the bearer may have been responsible for importing the disease into Malta. The other British surnames are of Maltese choreic wives of normal British husbands.

Prevention and Treatment

There is no cure for Huntington's Chorea. Surgical treatment is ineffective and we can only hope to alleviate, by means of drugs, the hyperkinesis of the choreic variety. We have, however, no means of preventing, arresting or reversing the mental deterioration.

Among the drugs that are employed, reserpine and the phenothiazines (such as trifluoperazine and dartalan) have been found most useful in reducing the choreic movements (31).

As there is no doubt that the disease is of a hereditary nature, the only logical and effective measure to combat its spread is to prevent its propagation by carriers (i.e. eugenic control). Theoretically the

only sure way of dealing with this disease and of safeguarding future generations is the sterilization of all persons vulnerable to the illness and not only of those who are already suffering from chorea. The reasons for casting this wide net are:

a) although certain personality traits, physical characters and EEG findings have been observed to herald the development of the disease, there are actually no reliable means of identifying at an early age those who harbour the gene from the non-carriers of it (32) as can be done in other genetically determined conditions such as thalassaemia minor and phenylketonuria (33);

b) although it is true that Huntington's Chorea is produced by a lethal gene, i.e. a gene that kills its own carrier, the clinical manifestations appear so late in life in the majority of cases (34) that those carrying the gene are already married and with offspring before the malady declares itself.

In practice, however, there are psychological, ethical and religious objections to sterilization which present unsurmountable obstacles to the adoption of eugenic control. On the psychological side the strongest barrier one has to face is the parental instinct, i.e. the desire of married couples of having children either because of an innate fondness for them or because of the desire to have descendants for the retention of one's own property in one's own family.

The ethical factor and the religious convictions of the patient are equally formidable hurdles to overcome and must be respected. It is needless to remind you that for Catholics direct sterilization is unlawful and immoral. But these difficulties should not breed an attitude of fatalism and nihilism. In fact affected individuals and their children should be advised against marriage and infertile couples should not be encouraged to seek treatment for their sterility.

Thanks to the outlook of the Catholic Church with regard to family limitation it is now possible to help vulnerable parents to reduce the potential number of their offspring and thus diminish the inci-

dence of the disease. The Church does not oppose the spacing of births on medical and eugenic grounds but makes it lawful from the moral angle to use the safe period for this purpose not only "for a considerable period of time" but "even for the entire duration of the marriage" (35). Today we have appropriate facilities, such as the Cana Clinics, where advice and instruction on birth regulation are available (36).

Finally a few words about the need for notification of the disease. In the past the scope of notification was the quick detection of infectious illnesses so that prompt measures could be taken to stem their advance in time. Nowadays the aim of notification has been extended to obtain information about the prevalence of non-infectious diseases such as cancer and coronary thrombosis. It is only through a similar statutory notification of Huntington's Chorea to the Public Health Authorities that we can arrive at a reasonably accurate epidemiological picture of the pattern of morbidity of this disease in the Maltese Islands. I, therefore, suggest that Huntington's Chorea be made a notifiable disease.

In the pedigree plans a square stands for a male and a circle for a female; black stands for a sufferer from the illness.

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References

- GARRISON, F.H. (1963). An Introduction to the History of Medicine, Philadelphia, p. 187.
- GUTHRIE, D. (1947). A History of Medicine, Edinburgh, p. 100.
- OSLER, W. (1938) The Principles and Practice of Medicine, New York, p. 1370.
- OSLER, W. (1938), op. cit., p. 1200.
PENROSE, L.S. (1963) The Biology of Mental Defect, London, p. 135.
JELLIFFE, S.E. and WHITE, W.A. (1935). Dis-
- eases of the Nervous System, Philadelphia, p. 668.
- HAYMAKER, W. (Edit.). (1953). The Founders of Neurology, Springfield, p. 305.
- MAYER GROSS, W. (1960). Clinical Psychiatry, London, p. 495.
- HAYMAKER, W. (1935). op. cit., p. 305.
- LYON R.L. (1962) Brit. Med. J., *1*, 1301.
- BROTHERS, C.R.D. and MEADOWS, A.W. (1955). J. ment. Sci., *101*, 559 and 561.
- The Merck Manual of Diagnosis and Therapy (1957), Rohway, N.J., p. 1173.
- HENDERSON, D.K. and GILLESPIE, R.D. (1944). A Textbook of Psychiatry, Oxford University Press, p. 504.
- PENROSE, L.S. (1963). op. cit., p. 135.
- MINSKI, L. and GUTTMANN, E. (1938). J. ment. Sci., *84*, 21.
- OSLER, W. (1938), op. cit., p. 1200.
MINSKI, L. and GUTTMANN, E. (1938) op. cit., p. 21.
- CATHCART, J.P.S. *et al.*, (1961). Proceedings of the Third World Congress of Psychiatry, Montreal, p. 581.
- JELLIFFE, S.E. and WHITE, W.A. (1935). op. cit., p. 671.
- JELLIFFE, S.E. and WHITE, W.A. (1935), op. cit., p. 669.
MAYER GROSS, W. (1960), op. cit., p. 498.
- CRITCHLEY, M. (1960). The British Encyclopaedia of Medical Practice, Second Edition, London, Vol. 3, p. 479.
- PENROSE, L.S. (1963), op. cit., p. 135.
- JERVIS, G.A. (1963). Arch. neur. (Amer. Med. Ass.), *9*, 255.
- BITTENBENDER, J.B. and QUADFASEL, F.A. (1962) Arch. neur. (Amer. Med. Ass.), *7*, 283.
- COURVILLE, C.B. *et al.* (1963). Arch. neur. (Amer. Med. Ass.), *8*, 481.
- The Merck Manual, etc. (1957) pp. 1083 and 1073.
PORTER, H. (1964). Arch. neur. (Amer. Med. Ass.), *11*, 341.
- PENROSE, L.S. (1963), op. cit., p. 21.
MINSKI, L. and GUTTMANN, E. (1938), op. cit., p. 21.
BITTENBENDER, J.B. and QUADFASEL, F.A. (1962), op. cit., p. 283.
JERVIS, G.A. (1963), op. cit., p. 255.
MAYER GROSS, W. (1960), p. cit., p. 496.
- JELLIFFE, S.E. and WHITE, W.A. (1935), op. cit., p. 669.
- MAYER GROSS, W. (1960), op. cit., p. 496.
- JERVIS, G.A. (1963), op. cit., p. 255.
- JERVIS, G.A. (1963), op. cit., p. 255 et seq.
BITTENBENDER, J.B. and QUADFASEL, F.A. (1962), op. cit., p. 283 et seq.
- BITTENBENDER, J.B. and QUADFASEL, F.A., op. cit.

- MINSKI, L. and GUTTMANN, E. (1938), *op. cit.*, p. 21 et seq.
24. MINSKI, L. and GUTTMANN, E. (1938), *op. cit.*, p. 21 et seq.
JELLIFFE, S.E. and WHITE, W.A. (1935), *op. cit.*, p. 670.
25. MINSKI, L. and GUTTMANN, E. (1938), *op. cit.*, p. 21 et seq.
26. MINSKI, L. and GUTTMANN E., *op. cit.*
COURVILLE, C.B. *et al.* (1963), *op. cit.*, p. 481.
JERVIS, G.A. (1963), *op. cit.*, p. 255 ta seq.
27. MINSKI, L. and GUTTMANN, E. (1938), *op. cit.*, p. 21 et seq.
BITTENBENDER, J.B. and QUADFASSEL, F.A. (1962), *op. cit.*, p. 283 et seq.
28. CATHCART, J.P.S. *et al.* (1961), *op. cit.*, p. 581 et seq.
29. JELLIFFE, S.E. and WHITE, W.A. (1935), *op. cit.*, p. 670.
30. JERVIS, G.A. (1963), *op. cit.*, p. 255 et seq.
BICKFORD, J.A.R. and ELLISON, R.M. (1935). *J. ment. Sci.*, 99, 292.
REID, J.J.A. (1960). *Brit. med. J.*, 2, 650.
31. FORREST, A.D. (1957) *J. ment. Sci.*, 103, 512.
LYON, R.L. (1962). *Brit. med. J.*, 1, 1308.
BAKER, A.B. (1962). *Clinical Neurology*, Sec. Edit., New York, p. 1317.
32. MINSKI, L. and GUTTMANN, E. (1938), *op. cit.*, p. 21 et seq.
MAYER GROSS, W. (1960), *op. cit.*, p. 4981.
33. ROBERTS, J.A.F. (1964). *Brit. med. J.*, 2, 1217.
34. GRUNEBERG, H. (undated). *Elementary Genetics*, Edinburgh, p. 20.
35. POPE PIUS XII (1960). *Address on Marriage and the Moral Law*, Catholic Truth Society, London, p. 19.
36. VELLA, C.C. (1964). *Times of Malta*, 12th January, p. 8.

THE MECHANISM OF ACID SECRETION BY GASTRIC MUCOSA

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The mechanism of acid secretion by gastric mucosa has been the subject of much experimentation and speculation in recent years. Many investigations in this field, including those described here, have been prompted by an idea which is generally known as the redox theory of acid secretion.

The redox theory was first proposed by Conway and Brady (1948). According to this theory the hydrogen ions secreted by the oxyntic cells of gastric mucosa come from the hydrogen atoms of the substrates of oxidative metabolism. One way of finding whether the hydrogen ions are so produced, is to determine the ratio between acid secretion and the associated oxygen uptake. If the hydrogen ions secreted by gastric mucosa are produced as a result of oxidoreductions in the oxyntic cells, one should not observe values greater than four for the ratio between acid secretion and the associated oxygen

uptake. This ratio is not expected to exceed four, because four is the maximum number of reducing equivalents which can combine with the oxygen molecule.

Much work has been carried out to find the value of the ratio between acid secretion and the associated oxygen uptake by gastric mucosa (Crane and Davies, 1951; Davenport, 1952; Bannister, 1964, 1965a). A central problem in this work is that one can only observe the total oxygen uptake of gastric mucosa, which must be divided in a justifiable way into the oxygen uptake associated with acid secretion, and that due to the non-acid-producing metabolism of the mucosa. It has been possible to achieve this end in isolated gastric mucosae of the frog (Bannister, 1963, 1965a).

The isolated gastric mucosa of the frog is a favourite preparation in the study of the biochemistry of acid secretion because the mucosa of a single stomach

is easy to isolate in one piece, and it survives for a long time and secretes acid *in vitro*. The rate of acid secretion by isolated frog gastric mucosae was found to be a linear function of their rate of oxygen uptake. This was a convenient finding because the ratio between acid secretion and the associated oxygen uptake is given by the slope of the line obtained on plotting acid secretion against oxygen uptake. A number of determinations indicated a mean value of 2.3 ± 1.0 (S.D.). It would seem that the value of the ratio between acid secretion and the associated oxygen uptake by gastric mucosa does not exceed four, as required by the redox theory of acid secretion (Bannister, 1965a).

The redox theory has two interesting consequences. In the first place, it implies a spatial separation of the hydrogen and hydroxyl ions produced in the respiratory chain. Secondly, it leads to the view that the secretion of hydrogen ions, unlike other active transport processes, does not necessarily require phosphate-bond energy.

Spatial separation of hydrogen and hydroxyl ions is demanded by the organization and function of the respiratory chain, which is located in the mitochondria. The respiratory chain transports hydrogen atoms and electrons from the substrates of oxidative metabolism to oxygen. The electron transport has the following general sequence: Substrate — pyridine nucleotide — flavoprotein — cytochromes — oxygen. The hydrogen atoms of the substrate being oxidized are released as hydrogen ions in the oxidation of flavoprotein. These hydrogen ions normally combine with hydroxyl ions produced as a result of reduction of oxygen at the terminal part of the respiratory chain.

It would appear that in the oxyntic cell there is a barrier which prevents hydrogen ions but permits electrons to flow from pyridine nucleotide and flavoprotein to the cytochromes (Bannister, 1965b). Acid secretion would seem to be possible only if hydrogen ions are produced on the pyridine nucleotide side of this barrier. If hydrogen ions are produced

on the cytochrome side, acid secretion does not take place because the hydrogen ions combine with the hydroxyl ions formed at the end of the respiratory chain.

This view was proposed because when electron transport in gastric mucosa is blocked by means of Amytal, which acts between pyridine nucleotide and flavoprotein, the ability to secrete acid is not restored by restoring electron transport in various ways at the stage of the cytochromes (Bannister, 1965b).

The hydrogen-ion barrier between flavoprotein and the cytochromes is formally equivalent to a *secretory membrane*. It would seem that a structural barrier exists rather than an energy-requiring process which prevents the translocation of hydrogen ions. The evidence for this idea comes from the mechanism of action of the so-called uncoupling agents.

The major mechanism of energy capture in the cell is the process of oxidative phosphorylation. Electron transport in the respiratory chain is associated with considerable release of energy. This energy is partially harnessed by the synthesis of so-called energy-rich bonds, which ultimately take the form of the terminal phosphate bond in adenosine triphosphate (ATP). Uncoupling agents prevent the synthesis of ATP by oxidative phosphorylation.

It has been known for some time that the classical uncoupling agent 2,4-dinitrophenol (DNP) inhibits acid secretion by gastric mucosa. It was thought that this action of DNP meant that hydrogen-ion secretion requires phosphate-bond energy. There is, however, evidence for an alternative view.

It has been shown that DNP catalyses the diffusion of hydrogen ions across biological membranes such as the mitochondrial membrane of animal cells and the plasma membrane of bacteria (Mitchell, 1966). This action would seem to be responsible for the inhibition of acid secretion by DNP (Bannister, 1965b, 1966b).

The efficiency of the secretory membrane, which has been postulated to exist in the oxyntic cell, is measured by the ratio between acid secretion and the asso-

ciated oxygen uptake. According to the redox theory, this ratio will have values varying from zero to four depending on the efficiency of separation of hydrogen and hydroxyl ions (Bannister, 1966a). The value of the ratio is greatly reduced by DNP.

Uncoupling agents which do not catalyse the diffusion of hydrogen ions across biological membranes should not affect the efficiency of acid secretion in relation to oxygen uptake. As a matter of fact, an uncoupling agent in this category, namely, oligomycin, was found to have no effect on the ratio between acid secretion and the associated oxygen uptake by gastric mucosa (Bannister, 1966b).

In summary, it would seem that separation of hydrogen and hydroxyl ions produced in the respiratory metabolism of the oxyntic cell is a basic feature of the mechanism of acid secretion by gastric mucosa. However, the exact source and site of origin of the hydrogen ions in the oxyntic cell remain to be found. Work on this problem is being carried out. It is

directed at finding the activity of the enzymes which could supply the acid secretory process with reducing equivalents, namely, the oxidoreductases.

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References

- BANNISTER, W.H. (1964). *Biochem. J.* *89*, 62P.
 BANNISTER, W.H. (1964). *Nature*, *203*, 978.
 BANNISTER, W.H. (1965a). *J. Physiol.*, *177*, 429.
 BANNISTER, W.H. (1965b). *J. Physiol.* *177*, 440.
 BANNISTER, W.H. (1966a). *Amer. J. Physiol.* *210*, 211.
 BANNISTER, W.H. (1966b). *J. Physiol.* *186*, 89.
 CONWAY, E.J. and BRADY, T.G. (1948). *Nature*, *162*, 456.
 CRANE, E.E. and DAVIES, R.E. (1951). *Biochem. J.*, *49*, 169.
 DAVENPORT, H.W. (1952). *Fed. Proc.* *11*, 715.
 MITCHELL, P. (1966). *Boil. Rev.*, *41*, 445.

THE ISOLATION AND STUDY OF MAMMALIAN ISLETS OF LANGERHANS

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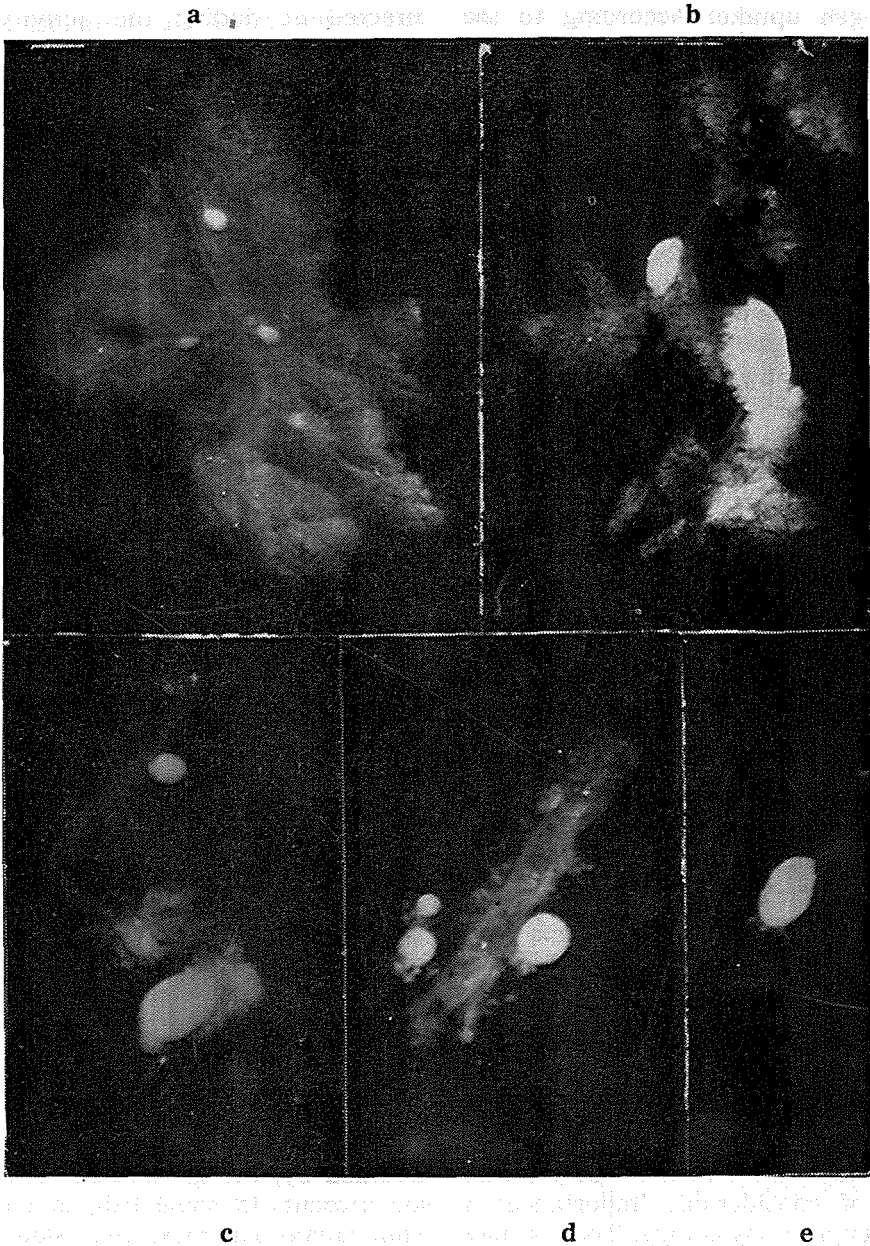
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The study of metabolism of isolated tissues is of considerable importance in biochemistry and physiology. Tissues may be studied as homogenates or slices, as cell cultured *in vitro*, or whole organs may be perfused. Pancreatic tissue, however, presents a particular problem. A homogenate of mammalian pancreas, for example, is representative of the acinar portion of the organ, but it is not very representative of the islets of Langerhans which constitute perhaps 1-2 percent of the pancreas. One can never be sure that any effect observed which is ascribable to the islets, is not either mediated through, or

modified by, the great bulk of acinar tissue present. In some fish, in contrast to mammalian pancreas, the islet tissue is segregated as a single body (the principal islet) from the diffuse acinar tissue, and several investigators have found fish a good source of islet cells for this reason (see Lazarow, 1963).

In the last two or three years several groups of workers have found it possible to isolate individual islets of Langerhans from mammalian pancreas, and by the use of micro-methods, to study their metabolism. It is the purpose of the present article to review some of the methods used by



Legend to Fig. I

Fig. 1. Micro-dissection of mouse pancreatic islets. (a) A thin piece of pancreas of a normal mouse. The islets are recognised as white spots disseminated along the ducts and blood vessels. (b) After teasing the tissue into smaller pieces, the islets are seen as spherical or ovoid bodies partly surrounded by acinar cells. (c) (d) Re-

moval of surrounding acini reveals intimate connections between islets and blood vessels. (e) A single islet has been isolated by cutting off its connections with the blood vessel. A few acinar cells remain at the lower pole. (Photograph kindly supplied by Dr. C. Hellerström).

myself and others, and to indicate some of the results obtained.

There are two methods by which mammalian islets of Langerhans can be isolated: (1) micro-dissection, and (2) selective enzyme treatment to loosen or remove much of the acinar tissue. These two methods will be considered separately, although it is sometimes advantageous to use both methods, that is, to digest with an enzyme prior to micro-dissection.

Micro-dissection

A method has been developed whereby fresh tissue is frozen solid, sections are cut with a microtome and are lyophilised; individual islets are then micro-dissected from the surrounding acinar tissues (Lowry, 1953; Lacy, 1962; Dixit, Lowe, and Lazarow, 1962; Kotoulas, Morrison, and Recant, 1965; Kotoulas and Recant, 1966). Such pieces of tissue have been used to study co-enzyme levels and certain enzyme systems believed to be connected with the synthesis of insulin. The enzymes of the tissue do not appear to be destroyed by this treatment, though the tissue can no longer be regarded as living. The implication must be that tissue prepared in this way is valuable material for enzyme studies, but cannot claim to represent tissue in its normal dynamic state.

Hellerström (1964) on the other hand, has reported encouraging results from micro-dissection of whole fresh pancreas (see Fig. 1). Watchmaker's forceps are used to pull out intact islets from the surrounding acinar tissue. The acinar tissue may be cut away with sharpened hypodermic needles, and the whole process is performed under the dissection microscope at 12-50 × magnification. The ease with which dissection is accomplished depends very much on the animal used. Mouse pancreas is the best material since the organ is thin and has comparatively large islets which stand out as whitish bodies against a pinkish acinar tissue. The pancreas of the congenitally obese-hyperglycaemic mouse has also been used as a source of islet tissue. The pancreas (and

the islets) in such animals is larger than in normal mice, and the islets are therefore correspondingly more easy to remove. Furthermore, Beta-cells comprise more than 90% of the cells in these islets. The metabolism of such islets is thus of particular interest, but until the specific defect causing the obesity and hyperglycaemia is better understood, it is perhaps wise not to consider the material identical with normal islets. Rat, guinea-pig, and rabbit pancreas may also be micro-dissected, but the process is made more difficult by several factors. These factors are the relatively greater thickness of the acinar tissue in which the islets are embedded, the small size and irregular shape of the islets, and the thinness of the capsule surrounding the islets. In the rat, removal of islets by micro-dissection is reported to be facilitated by ligation of the upper pancreatic duct 2-4 weeks before dissection (Keen, Sells, and Jarrett, 1965).

Attempts to reduce the bulk of mouse pancreas by drug treatment as opposed to ligaturing have so far met with little success. Dunnigan, Gagnon, and Berlinguet (1964) reported that an amino acid analogue, 1-aminocyclopentane carboxylic acid (ACPC), caused rapid atrophy of the acinar portion of rat pancreas without affecting the islets. We found (Wood and Smith, unpublished work) that in mice, the dose of this drug sufficient to cause a considerable amount of acinar atrophy was in the region of the lethal dose. In a group of six mice which were injected with ACPC in five daily doses of 0.25 mg. per gram body weight, all were very sick, and one of them died before the termination of the experiment. The amount of proteolytic enzyme activity present in homogenates of pancreas after activation of the zymogens was measured to obtain an indication of the amount of acinar tissue present. Although the total proteolytic enzyme activity was reduced to 20 percent of that of the pancreases of untreated controls, the pancreatic weights did not fall in the same proportion. The pancreases of the treated animals were consequently only marginally easier to micro-dissect.

Digestion with Enzymes

Micro-dissection has certain limitations. It is difficult to obtain more than 20-40 islets within 30 minutes of killing the animal. Furthermore, only with mouse and rat pancreas is it a reasonably easy task. To obtain (a) larger amounts of tissue, and (b) islets from other species, digestion of the pancreas with enzyme appears to be the best method. In order to obtain islets of Langerhans for culture *in vitro*, Moskalewski (1965) treated guinea pig pancreas with bacterial collagenase. In a preliminary report, Kostianovsky and Lacy (1966) described how 200-300 islets could be obtained from normal rat pancreas by digesting with collagenase. The acinar parenchyma is initially disrupted by injecting physiological medium into the pancreatic duct, and after digestion, the islets are obtained by sedimentation or centrifugation (see also Lacy and Kostianovsky, 1967). A modification of this method was used by Howell and Taylor (1966) for the isolation of rabbit islets.

Collagenase seems to be the only enzyme that can be used in these isolation procedures. In order to obtain intact islets by enzyme digestion, the enzyme chosen must break up the acinar tissue into single cells or small clumps of cells, but must leave intact the delicate capsule surrounding the islets. We have investigated (Wood and Smith, unpublished) several proteolytic enzymes under a variety of conditions. Trypsin and Chymotrypsin appear to have very little effect on mouse pancreas, whereas papain and several bacterial proteinases caused a great deal of digestion but were not selective, i.e. the islet as well as the acinar tissue was destroyed. The extent of digestion with collagenase depended on the rate of shaking or stirring during incubation as well as on the concentration of collagenase. On a shaker 30-60 minutes digestion at 37°C was required, but the time could be as short as 5-10 minutes if the mixture was stirred rapidly. It was found best to use a flat-bottomed test tube of 3 cm. diameter which contained a magnetic stirrer slightly less than 3 cm. in length. If the

period of digestion was prolonged unduly under these conditions, the islets themselves were eventually disrupted. It was therefore necessary to take samples of the digest at intervals and to examine them under the dissection microscope in order to judge when sufficient digestion has taken place.

It was advantageous to use different digestion procedures with the pancreases from different species. With mouse pancreas, a gentle collagenase digestion could be used to weaken the acinar tissue after which micro-dissection became very easy. On the other hand, for rabbit and guinea-pig pancreas, a vigorous digestion gave the best results. After washing in cold medium the islets were allowed to sediment, and then, under the dissection microscope, were picked out with a fine pipette. Several hundred islets could be obtained in about 30 minutes by this method. The treatment of pancreas prior to digestion is important. As described by Howell and Taylor (1966), the pancreas is distended by local injection of buffered medium through a fine needle at several sites at random. This procedure appears to separate the lobes of acinar tissue and makes the pancreas more susceptible to the action of collagenase. After this treatment the organ is cut into small pieces and is incubated with collagenase.

With a little practice it is not difficult to identify the individual, freed islets in a digestion mixture. However, if there is any doubt, a sample of the digest may be treated with dithizone solution. This compound stains islet tissue brick red, acinar tissue faintly orange, and adipose cells deep green. It is interesting that the islets of the guinea pig could not be stained by this method: this presumably reflects either the amount, or the state, of zinc in these islets, in contrast to mouse, rat, and rabbit islets (*cf.* Maske, 1957).

Islet Tissue Metabolism

There is abundant evidence that islets obtained by these methods are in a state which closely resembles their state *in vivo*. They survive the tissue culture (Moskalewski, 1965); they respire normally (Hel-

lerström, 1966); they synthesise insulin, and the insulin synthesis is stimulated by glucose (Howell and Taylor, 1966; Martin and Gagliardino, 1967). Islets obtained from hypophysectomised rats show impaired insulin synthesis unless the rats are given growth hormone (Martine and Gagliardino, 1967). Certain problems arise when dealing with such small amounts of tissue as a few islets. A single islet may have a dry weight of between 1 and 10 μg ., and so micro-methods must be used to follow the metabolism of isolated islets. Hellerström (1966) used a Cartesian diver microbalance to measure the respiration of a single islet. Other workers have employed radio-isotope methods because of their sensitivity and accuracy.

A single pancreatic islet is a fragile structure, and a light touch with a sharp needle is enough to rupture the containing membrane and release the cells. Pipettes used for transferring islets into incubation vessels must therefore have no sharp edges. Alternatively islets may be transferred with watchmaker's forceps. During micro-dissection it is advisable to leave the islets attached to small pieces of capillary by which they can be handled. If a homogenate of islet tissue is required, the micro-homogeniser described by Eichner (1966) should prove valuable. A loop of fine wire is driven inside a capillary tube by means of a dental drill. In this apparatus, it is claimed, a very few cells can be homogenised without loss of material.

Finally some consideration needs to be given to the problem of weighing islets or of finding their protein content. One can pick out islets for a given experiment so that they are all of approximately the same size. Nevertheless it is clearly desirable to be able to express results in terms of dry weight or protein content. Islets can be weighed on a quartz fibre ultra-microbalance after they have been dried on a piece of platinum foil, and this is probably the only reliable method for measuring the size of islets, though it is a destructive method, in that after drying, the islets are useless for other purposes.

It is clear that isolated islets of Langerhans obtained by the methods des-

cribed are amenable to study by suitable micro-methods. Moreover, it is encouraging that the results obtained so far are in accord with our earlier knowledge of endocrine pancreatic function. A future problem may be that even isolated islets do not contain a single cell type. Though the largest proportion of cells in islets are beta-cells, alpha-cells and other cell types are also present. It is possible that future techniques may provide us with pure preparation of beta-cells.

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References

- DIXIT, P.K., LOWE, I., LAZAROV A., (1962), *Nature* 195, 388.
- DUNNIGAN, J., GAGNON, P.M. and BERLINGUET, L., (1964), *Biochem. Pharmacol.*, 13, 517.
- EICHNER, D., (1966), *Experientia*, 22, 620.
- HELLERSTRÖM, C., (1964), *Acta Endocrinol. (Copenhagen)* 45, 122.
- HELLERSTRÖM, C., (1966), *Biochem. J.*, 98, 7C.
- HOWELL, S.L. and TAYLOR K.W., (1966), *Biochim. Biophys. Acta*, 130, 519.
- KEEN, H., SELLS, R. and JARRETT, R.J., (1965), *Diabetologia*, 1, 28.
- KOSTIANOVSKY, M. and LACY, P.E., (1966), *Fed. Proc.*, 25, 377.
- KOTOULAS, O.B., MORRISON, G.R. and RECENT, L., (1965) *Biochim. Biophys. Acta*, 97, 350.
- KOTOULAS, O.B. and RECENT, L., (1966), *Proc. Soc. Exp. Biol. Med.*, 122, 1228.
- LACY, P.E., (1962), *Diabetes*, 11, 96.
- LACY, P.E. and KOSTIANOVSKY, M., (1967), *Diabetes* 16, 35.
- LAZAROV, H., (1953), *Recent Progr. in Hormone Res.* 19, 489.
- LOWRY, O.H., (1953), *J. Histochem. Cytochem.*, 1, 420.
- MARTIN, J.M. and GAGLIARDINO, J.J., (1967), *Nature*, 213, 630.
- MASKE, H., (1957), *Diabetes*, 6, 335.
- MOSKALEWSKI, S., (1965), *Gen. comp. Endocrinol.*, 5, 341.

INDUCED DRUG METABOLISM

STUDIES WITH INDOLIC SUBSTRATES

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The oxidative enzymes which metabolise drugs and foreign substances are associated with the endoplasmic reticulum of the parenchymal liver cell. Their physiological role in "detoxication" appears to be related to the change in polarity which they bring about in the case of lipid soluble compounds before these can be eliminated through the renal tubule (Brodie, 1964). Ring hydroxylation of aromatic molecules is the main mechanism whereby this change in solubility is effected; at the same time hydroxylation renders the compound susceptible to further modification through conjugative processes. The enzyme systems reside in the pellet resulting from high speed centrifugation (100,000 × g) of the mitochondrial supernatant of liver homogenates. This pellet which constitutes the microsomes consists of membranes with or without ribosomes; the oxidative activity is associated with the smooth membranes (Ernster *et al.*, 1962).

The effect of treating experimental animals with various drugs on the yield of oxidation products of other pharmacologically active substances has been reviewed (e.g. Conney and Burns, 1962). This paper will summarise the effect of pretreatment on indole metabolism with particular reference to lipid soluble tryptamines which are 6-hydroxylated (Jepson *et al.*, 1962) by a liver microsomal system requiring reduced nicotinamide adenine dinucleotide phosphate and molecular oxygen in common with the drug metabolising enzymes (Jaccarini, 1966).

Methods

Wistar albino rats and English white rabbits were injected intraperitoneally

daily with inducing agent in a suitable solvent. Controls were given solvent only. The animals were kept on normal diets with free access to water. After the last injection they were starved for 24 hours and killed. Microsomes were isolated according to Mitoma *et al.* (1956), and incubated with substrate in the presence of NADP, nicotinamide, ATP and Mg ions in pyrophosphate buffer pH 7.2 at 37.5 C for one hour in open vessels. 6-Hydroxy products were estimated through the pink colour (515 millimicron) given by the deproteinised incubate with diazotised sulphanilic acid. For "in vivo" work, the animals were kept singly in cages and the urines were collected after 5 hours and after 24 hours from each injection. Metabolites were identified and their abundance estimated by thin layer chromatographic techniques.

Results and Discussion

All the agents used had a stimulating effect with the exception of ethionine in combination with methylcholanthrene and carbon tetrachloride (*Table I*). Ethionine is a known inhibitor of protein synthesis through its effect on liver ATP (Villa-Trevino *et al.*, 1963). Carbon tetrachloride in dosage as used by Cameron and Karunaratne (1936) destroyed all the hydroxylating capacity with respect to diethyltryptamine.

Normally poor substrates for 6-hydroxylation such as acetyltryptophan were the ones which suffered the greatest stimulation with phenobarbitone. The same effect was obtained in the case of the carcinogenic hydrocarbons, benzpyrene and methylcholanthrene; whilst tryptamine is normally a poor substrate for rat

TABLE I
The Effect of Pretreatment on "in vitro" Hydroxylation

<i>Pretreatment</i>	<i>Animal</i>	<i>Substrate</i>	<i>Percentage Stimulation of Hydroxylation</i>
Phenobarbitone	Rat	Tryptamine	22
Phenobarbitone	Rat	N, N-diethyltryptamine	18
Phenobarbitone	Rat	N-acetyltryptophan	31
3,4-benzpyrene	Rat	Tryptamine	25
3,4-benzpyrene	Rabbit	Tryptamine	7
3-methylcholanthrene	Rat	N, N-dimethyltryptamine	5
3-methylcholanthrene	Rabbit	N,N-dimethyltryptamine	34
Tryptamine	Rat	Tryptamine	41
Tryptamine	Rabbit	Tryptamine	12
Ethionine and 3-methylcholanthrene	Rat	Tryptamine	0
Testosterone	Rat (female)	N, N-diethyltryptamine	25
Carbon Tetrachloride	Rat	N, N-diethyltryptamine	complete inhibition.

microsomes, it is very active with rabbit microsomes and the opposite effects hold for the alkyltryptamines; *Table I* shows the reciprocal stimulatory effect on the normal species dependent substrate activity. It is possible, therefore, that both phenobarbitone and the polycyclic hydrocarbons improve the penetration of poor substrates to the active site of the enzyme.

The effect of testosterone indicates that some similarity between the interaction of indolic substrates and steroids with the microsomal system might exist especially since phenobarbitone is known to enhance the hydroxylation of testosterone (Conney and Klutch, 1963) and other anabolic steroids.

Both tryptamine and diethyltryptamine (*Table II*) stimulated their own metabolism.

No single mechanism can be postulated for the inducing effect of the various substances used. In many cases liver enlargement occurred accompanied by the proliferation of the smooth endoplasmic reticulum (Orrenius, 1965). However, anabolic steroids do not produce liver enlargement (Fouts, 1963). Moreover, differential enzyme stimulation also occurs (Creaven *et al.*, 1964). The general finding that a drug is capable of stimulating its

own metabolism affords a rationalisation of tolerance and sensitivity. It is likely that drug interactions will be explained at the level of microsomal activity and predictions will be made on this basis.

TABLE II
The Effect of Pretreatment on Urinary Hydroxy Metabolites in the Rat

<i>Day</i>	<i>Treatment</i>	<i>Relative Abundance of Hydroxy Metabolites</i>
1st	N, N-diethyltryptamine	+
2nd	N, N-diethyltryptamine	+
3rd	N, N-diethyltryptamine	++
4th	N, N-diethyltryptamine	++
1st	3-methylcholanthrene	-
2nd	3-methylcholanthrene	-
3rd	N, N-diethyltryptamine	++++
4th	N, N-diethyltryptamine	++++
5th	N, N-diethyltryptamine	+

Summary

Stimulation of indole 6-hydroxylation "in vivo" and "in vitro" is effected through the administration of phenobarbitone,

polycyclic carcinogens and 6-hydroxyase substrate to rats and rabbits.

References

- BRODIE, B.B. (1964), *The Pharmacologist*, 6, 12.
 CAMERON, G.R. and KARUNARATNE, W.A.E. (1936), *J. Path. Bact.*, 42, 1.
 CONNEY, A.H. and BURNS, J.J. (1962), *Advances in Pharmacology*, Garrattini and Shore, Eds., Academic Press, New York, 1, 31.
 CONNEY, A.H. and KLUTCH, A. (1963), *J. Biol. Chem.*, 238, 1611.
 CREAVEN, P.J., PARKE, D.V. and WILLIAMS, R.T. (1964) *Biochem. J.*, 91, 12P.
 ERNSTER, L., SIEKEVITZ, P. and PALADE, G.E. (1962), *J. Cell. Biol.*, 15, 541.
 FOUTS, J.R. (1963), Personal communication in *Progr. Drug. Res.*, 6, 13.
 JACCARINI, A. (1966), Ph.D. Thesis, University of London.
 JEPSON, J.B., ZALTZMAN, P. and UDENFRIEND, S. (1962), *Biochim. Biophys. Acta*, 62, 91.
 MITOMA, C., PCSNER, H.S., REITZ, H.C. and UDENFRIEND, S. (1956), *Arch. Biochem. Biophys.*, 61, 431.
 ORRENIUS, S. (1965), *J. Cell. Biol.*, 26, 713.

SCIENCE (MAINLY MEDICAL) AND LITERATURE (MAINLY MEDIAEVAL)

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(This oration was delivered on St. Luke' Day 1966, under the auspices of the Malta Branch of the British Medical Association. The Branch has, since a number of years, invited an eminent layman to address it on this occasion.)

There are three things I should like to say before I begin my talk — "Science (mainly medical) and Literature — (mainly mediaeval)." First, how highly pleased and deeply honoured I am to have been invited to deliver the St. Luke's lecture to the Malta Branch of the British Medical Association. Secondly, how fitting it is to be able to dedicate a medico-literary lecture with such a title and such a content to St. Luke — himself the doctor-evangelist who is remembered more for his writing than for his doctoring. And thirdly I would ask you to bear with me if I seem to have a bee in my bonnet about this particular topic: for months I have been looking for an excuse — and a captive audience — so that I could deliver this particular lecture. And now that both the occasion and the audience have been given to me, I have some qualms that

those of you who anticipate an amusing talk of popular appeal are going to be sadly disappointed. But I had no hesitation in picking my subject. Contacts between medicals and literati are few in the present age; Brett Young and Cronin gave up practice when they became writers. Indeed, I had an experience, a couple of years ago, that will show how far apart medicine and literature have grown. I was meeting my External Examiner at the airport when one of my medical colleagues was meeting his. He introduced him to us as a scholar eminent in the field of Brucellosis, "What's that?" asked my external examiner, "Is it a disease of sprouts?"

What I have done, therefore, is to go straight back to the 14th century, when all forms of intellectual activity were much more closely integrated than they are today, over-specialisation had not yet reared its ugly head, and the complete man was not expected to be a scientific ignoramus just because he was a literary genius. And I have chosen for my starting-point Chaucer's portrait of the Doctor in the *General Prologue to the Canterbury Tales*. From

this portrait I shall develop my entire thesis, and I am going to read it to you twice — first in Chaucer's original pronunciation and then, more comprehensively, in Nevil Coghill's modernised version:

“With us ther was a DOCTOUR OF PHISIK;
 In al this world ne was ther noon hym lik,
 To speke of phisik and of surgerye,
 For he was grounded in astronomye.
 He kepte his pacient a ful greet deel
 In houres by his magyk natureel.
 Wel koude he fortanen the ascendent
 Of his ymaget for his pacient.
 He knew the cause of everich maladye,
 Were it of hoot, or coold, or moyste, or drye
 And where they engendred, and of what humour.
 He was a verray, parfit praktisour;
 The cause yknowe, and of his harm the roote,
 Anon he yaf the sike man his boote.
 Ful redy hadde he his apothecaries
 To sende hym drogges and his letuaries,
 For ech of hem made cother for to wynne —
 Hir friendshiphe nas nat newe to bigynne.
 Wel knew he the olde Esculapius,
 And Deyscorides, and eek Rufus,
 Olde Ypocras, Haly, and Galyen,
 Serapion, Razis, and Avycen,
 Averrois, Damascien, and Constantyn,
 Bernard, and Gatesden, and Gilbertyn.
 Of his diete mesurable was he,
 For it was of no superfluitee,
 But of greet norissyng and digestible.
 His studie was but litel on the Bible.
 In sangwyn and in pers he clad was al,
 Lyned with taffata and with sendal;
 And yet he was but esy of dispence;
 He kepte that he wan in pestilence.
 For gold in phisik is a cordial,
 Therefore he lovede gold in special.”

Coghill:

“A *Doctor* too emerged as we proceeded:
 No one alive could talk as well as he did
 On points of medicine and of surgery,
 For, being grounded in astronomy,
 He watched his patient's favourable star,
 And, by his Natural Magic knew what are
 The lucky hours and planetary degrees
 For making charms and magic affigies.
 The cause of every malady you'd got
 He knew, and whether dry, cold, moist or hot;
 He knew their seat, their humour and condition.
 He was a perfect practising physician.
 These causes being known for what they were,
 He gave the man his medicine then and there.
 All his apothecaries in a tribe
 Were ready with the drugs he would prescribe

And each made money from the other's guile;
 They had been friendly for a goodish while.
 He was well-versed in Aesculapius too
 And what Hippocrates and Rufus knew
 And Dioscorides, now dead and gone,
 Galen and Rhazes, Hali, Serapion,
 Averroes, Avicenna, Constantine,
 Scotch Bernard, John of Gaddesden, Gilbertine.
 In his own diet he observed some measure;
 There were no superfluities for pleasure,
 Only digestives, nutritives and such.
 He did not read the Bible very much.
 In blood-red garments, slashed with bluish-grey
 And lined with taffeta, he rode his way;
 Yet he was rather close as to expenses
 And kept the gold he won in pestilences.
 Gold stimulates the heart, or so we're told.
 He therefore had a special love for gold.”

There are enough points of interest here to last us many lectures: but most of them I must pass by with a mere mention, since they are incidental to my present purpose. A Maltese audience will naturally remark how Chaucer's Doctor had his own apothecaries, with whom he associated closely in business to their mutual advantage; how like Malta this is, where the doctor usually has consulting rooms inside a pharmacy. Or notice the dependence on AUTHORITY rather than experience or experimentation — typically mediaeval: and how the authorities themselves divide into three groups — classical, Arabic of the 10th and 11th centuries, and near-contemporary British medical writers. Or we could talk about the Black Death which decimated Europe in Chaucer's boyhood and recurred on frequent occasions during his lifetime: and how the physicians used to put drops of gold into their prescriptions to drive the prices up — how unlike present practice!

“Since gold in phisik is a cordial,
 Therefor he loved gold in special.”

But I must press on to the first of my main areas of discussion — the strange fact that a 14th century doctor had to be grounded in astronomy. I wonder how many of my medical colleagues in the University would welcome the inclusion of a paper in astronomy in the syllabus of the Faculty of Medicine and Surgery?

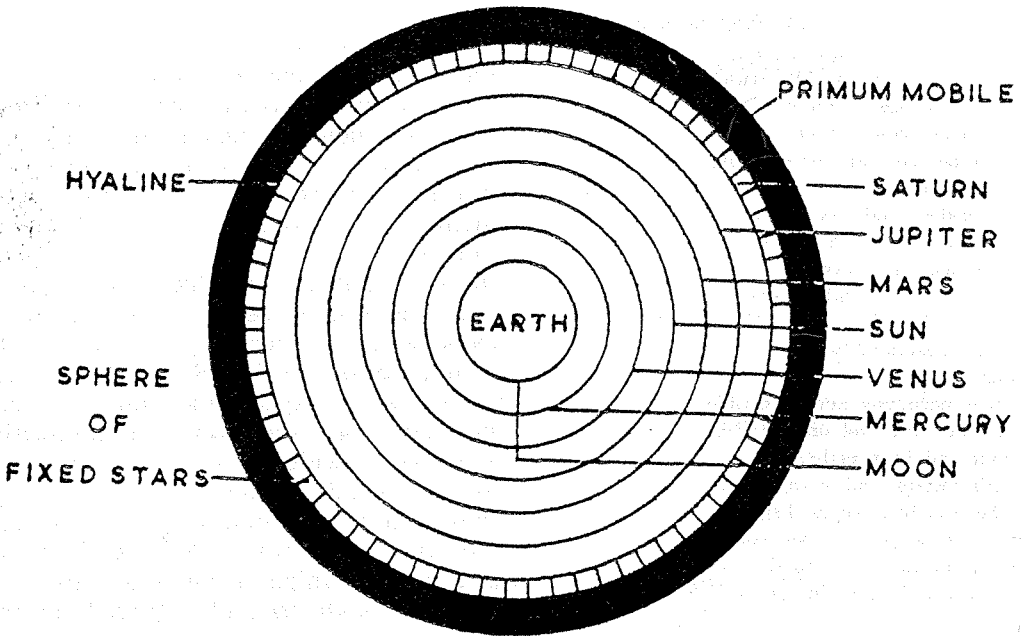
May I call your attention to the accompanying sketches:

The first sketch represents the Ptolemaic system of astronomy, universally accepted by the Christian world of the Middle Ages. The Earth was the centre of the Universe, and it was surrounded by the concentric orbits of the seven known planets — Saturn farthest away, then Jupiter, Mars, the Sun, Venus, Mercury and the Moon. Beyond Saturn was the sphere of the Fixed Stars, and the whole Universe was encased in a jacket

Activated by the Primum Mobile, each sphere — or rather the atmosphere of each sphere — impinged on the one next inside it and set it too in motion. The friction set up by this interaction resulted in a note of music, and the total result of the interaction of all the atmospheres was the celestial octave, the heavenly harmony, or the Music of the Spheres.

In the Middle Ages, two methods were used for measuring time: first, the day was divided into twenty-four equal hours, — the hours of the natural day; secondly,

THE EMPYREAN



of water — the hyaline or Waters of the Firmament, the water left over after God had put water on the earth and under the earth. This jacket insulated the universe from extremes of cold and heat. Far beyond, in the Empyrean, sat God on His throne, hidden by cloud and fire and supported by four Seraphim. His love for mankind flowed down into the universe, and was transformed into energy by the Primum Mobile, or First Mover; so that the Middle Ages literally believed that it was love that makes the world go round: for should God cease to love man, the world would grind to a fatal standstill.

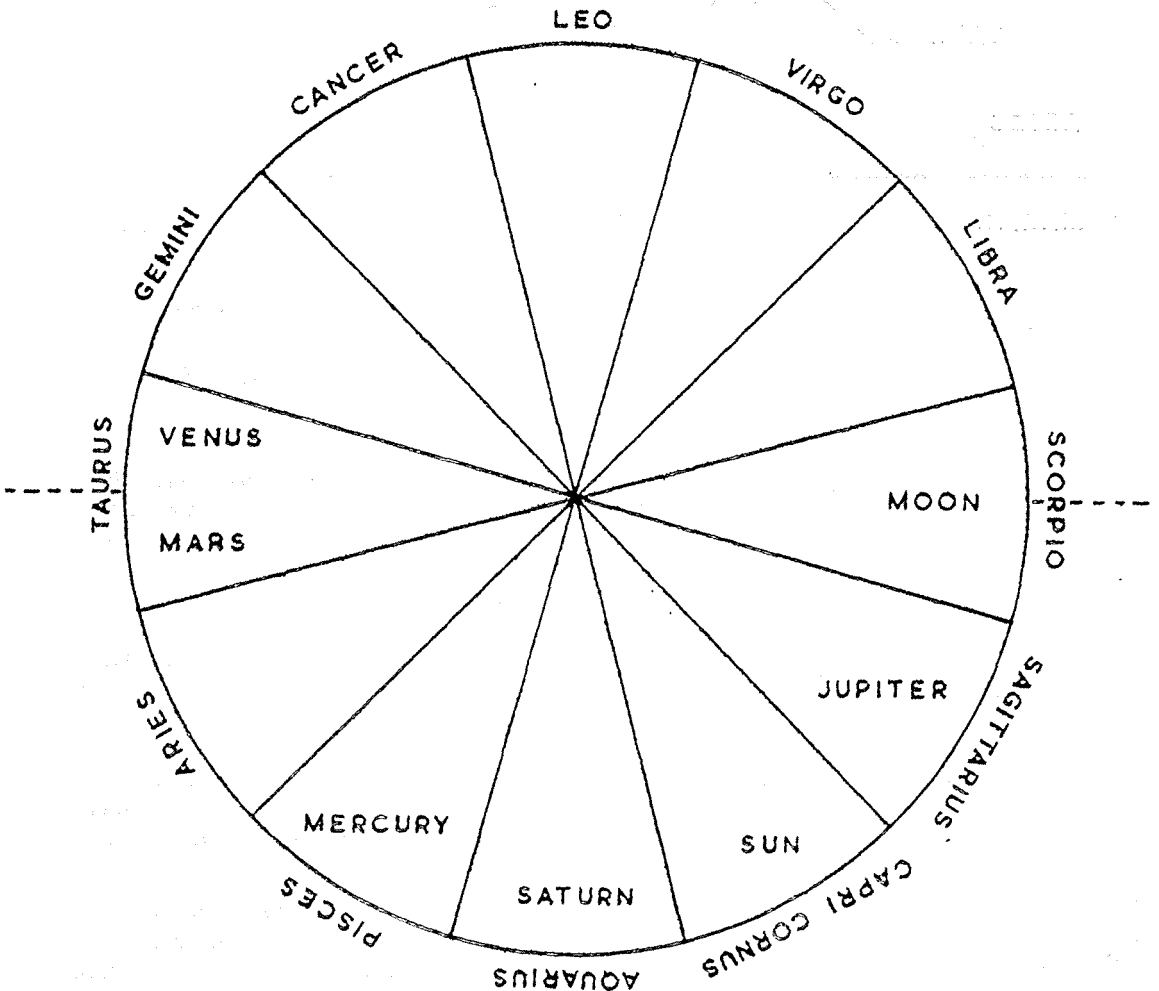
the period between dawn and sunset was divided into twelve equal parts, and the period between sunset and dawn likewise, — the hours of the artificial day, or Hours of the Planets. Each artificial hour, beginning with the first after dawn, was given to one of the planets, and the astrological influence of that planet ruled supreme in that hour. The theory was that God had finished making the world on the sixth day — on March 12th about four thousand years B.C.; the first hour of the day was therefore given to Saturn, and the day was named after him — *Saturni dies*. Saturn ruled the first hour, Jupiter the

second, and so on with Saturn controlling the eighth, fifteenth and twenty-second hours of the first day. The twenty-fifth hour belongs to the Sun, — but this is the first hour of the second day, which is therefore called *Sun-day*. Similarly with Moon-day, or Monday. In naming the remaining days, the English deserted the classical in favour of the Norse gods Tiu, Woden and Thor, and the goddess Freya, but French and Italian show the normal development — *Mardi, Martedì; Mercredi, Mercoledì; Jeudi, Giovedì; Vendredi, Venerdì*.

This process of the naming and ordering of the days of the weeks underlines two points: the importance of mediaeval

studies to a comprehension of some of the most basic and commonplace ideas of the present day: and the variety of the English cultural heritage — here are Egyptian astronomy, Classical and Norse mythology all mixed together.

The astrological influence exerted by the various planets was in keeping with their classical character — Venus was for love and Mars for war. Their influence on man varied, not merely according to the day and the hour, but to their positions in the heavens, relative to one another and also to the Zodiac through which they passed. The next sketch shows, in a simplified form, the inter-relationship of planetary influences:



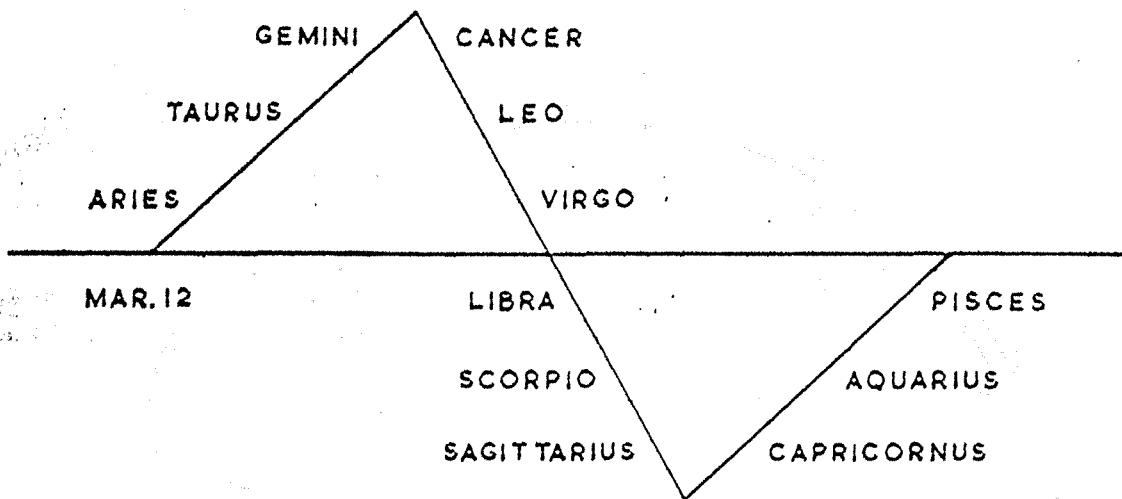
At the moment of birth, the sign of Taurus is rising over the horizon, and in it are Venus and Mars — in conjunction. The child will therefore be both amorous and aggressive: because Taurus is a sign in which Mars is more powerful than Venus, the child will be more aggressive than amorous, but the Moon, a chaste influence, is in opposition, a very bad relationship, so that the subject will be unchaste into the bargain. The horoscopic possibilities are manifold!

Let us look at the signs of the Zodiac in another sketch:

If we believe, as the Middle Ages did,

plest, he uses the heavens to tell the time of the day and of the year:

“Whan that the month in which the world bigan
That highte March, when God first makid man,
Was compleet, and passed were also,
Syn March bigan, thritty dayes and two,
Bifel that Chauntecleer in al his pryde,
His sevene wyves walkynge by his syde,
Caste up his eyen to the brighte sonne,
That in the signe of Taurus hadde yronne
Twenty degrees and oon, and somewhat moore,
And knew by kynde, and by noon oother loore,
That it was pryme, and crew wth blisful stevene.
‘The sonne,’ he seyde, ‘is clomben up on hevene
Fourty degrees and oon, and moore ywis’.”



that the Earth is stationary, the Sun crosses the Equator at the vernal equinox, moves northwards until mid-summer, and turns south again at the tropic of cancer, $23\frac{1}{2}^{\circ}$ N. of the Equator. The date of 12th instead of 21st March is because the Julian calendar, in use in Chaucer's day, was already 9 days wrong, and became 11 days in error before Parliament decreed a change-over to the Gregorian calendar in 1752. When the people of London heard that they were to go to bed on 1st September and wake up on the 13th, they broke the windows of the Houses of Parliament, shouting: "Give us back our eleven days!"

What literary use does Chaucer make of all this Scientific material? At its sim-

Chaucer tells us here that March is over, and that another 32 days have passed since then — i.e. the 30 of April and 2 more: so that the date is his favourite one of 3rd May. He also tells us that the sun had run just over 21° in the Zodiacal sign of Taurus. We know that, according to Chaucer's calculations, the Sun entered Aries on 12th March and moved at about 1° per day — 360° in 365 days: it would thus enter Taurus on 11th April, a further 21° would bring it to the 2nd of May, and the "somewhat moore" would again give us the same date of 3rd May.

But this is not the sum of Chauntecleer's preternatural brilliance. He may know by instinct that it is nine o'clock in the morning, but he can also establish the

fact scientifically: he claims that the angle of elevation of the Sun is just over 40° . It has actually been calculated, from nautical tables, that the angle of the Sun at 9 a.m. on 3rd May, 1387, in the latitude of Greenwich was 41° !

Secondly, Chaucer uses his knowledge of the stars for astrological purposes: astronomy is the Science of the stars, astrology is the connection of starlore to its influence on mankind. The three principals in *The Knight's Tale* go to beg for success in the hour most propitious to the relevant tutelary deity. First, Palamon:

"That Sunday night ere day began to spring
There was a lark which Palamon heard sing
(Although two hours before the day came on,
Yet the lark sang, and so did Palamon).
With holy heart and in a lofty mood
He rose on pilgrimage and he pursued
His path to Citherea, the benign
And bl'ssful Venus, to her honoured shrine.
And in her hour, among the early mists,
He stepped towards her Temple in the lists
And down he knelt in humbleness and fear
With aching heart, and said as you shall hear."

Next Emily:

"In the third hour after Palamon
Had sought out Venus for his orison,
Up rose the sun, and up rose Emily
And hastened to Diana's sanctuary."

And finally, Arcite:

"Now in the hour of Mars next after this
Arcite rose up and sought the edifice
Of fiery Mars, to do beneath his banner
His sacrifice, as was the pagan manner."

Palamon got up very early to visit the temple of Venus *in her hour*, because then she could have more power to grant his prayer. According to our previous calculations, the twenty-fourth hour of Sunday is governed by Mercury, and the twenty-third by Venus: it is exactly then, two artificial hours before dawn on the Monday, that Palamon importunes Venus for success in love. Emily, as we might expect, rises at dawn to pray for Diana, but enjoys less success than she deserves considering that it is not merely Diana's hour but her day as well. Alcite also is

careful to wait for an astrologically opportune moment to address his plea to Mars: and he enjoys the added advantage that the tournament has been fixed for a Tuesday.

If we look at these passages with any care at all, we cannot fail to be convinced that both Chaucer and his audience were thoroughly familiar with this business of planetary influence.

Thirdly, Chaucer dabbles in Horoscopy — the relationship between the behaviour, actions and destiny of a character in relation to what is the pattern of the stars at the moment of his birth. Constance in the *Man of Law's Tale* would never have been allowed to embark on her journey at such a time — Chaucer tells us — had there been a competent astrologer in her father's Court. Best of all is the Wife of Bath, who is amorous because Venus was in the ascendant when she was born, and has consequently had five husbands and is now looking for a sixth; but because Mars was in conjunction with Venus at the moment of the wife's birth, she is aggressive as well as amorous, preaches and practises the gospel of woman's sovereignty in marriage, and is looking for a sixth husband solely because she has driven the other five into their graves.

Fourthly, Chaucer uses his astronomy for medical purposes. His doctor, as we have seen, is well grounded in astronomy. When he is called in, he brings his charts, not a black bag, and his interest is in exactly when his patient was born and what the disposal of the heavenly forces then was, at what precise moment he was taken ill, and what his dreams are. Then he will make his calculations, find out when the planets which are particularly influential on his patient's destiny are in favourable aspects, and then administer the medicine in a spoon of a metal suitable to the dominant planetary influence. Needless to say, by the time a propitious moment to administer the medicine had arrived, the patient had frequently died! Or the doctor might decide to make images and indulge in a little sympathetic magic, or he might resort to bleeding his patient if he thought that his humorous condition warranted it.

We must now leave Astronomy for our second area of discussion, the doctrine of the Four Humours; so let us see how the portrait of the Doctor continues:

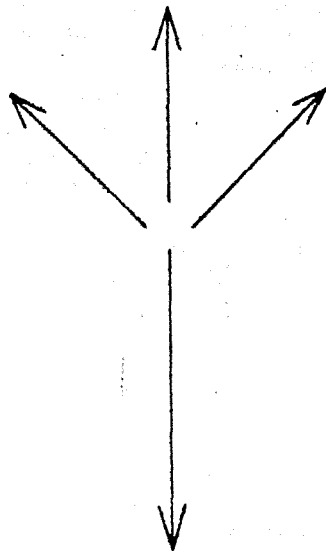
"For, being grounded in astronomy,
He watched his patient's favourable star
And, by his Natural Magic, knew what are
The lucky hours and planetary degrees
For making charms and magic effigies.
The cause of every malady you'd got
He knew, and whether dry, cold, moist or hot;
He knew their seat, their humour and condition.
He was a perfect practising physician."

The doctrine of the four humours was central to mediaeval — and even Renaissance — medicine. It is a simple concept, which postulates that, in health, the human body maintains a perfect balance between two pairs of opposed forces, as below.

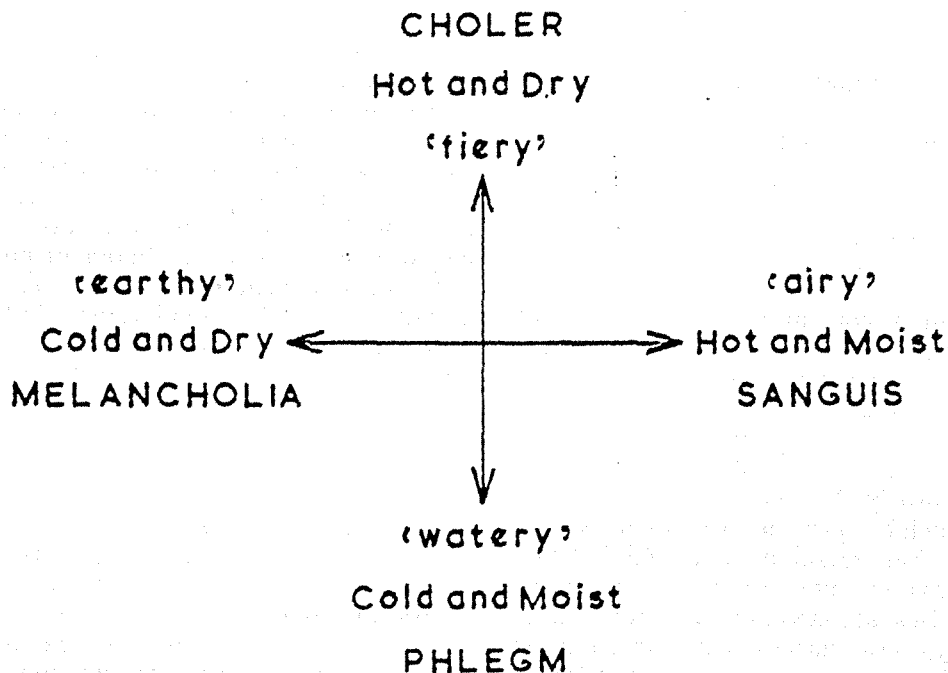
An excess of one of these humours upsets the balance; Chaunticleer, according to Pertelote, suffers from an excess of cholera, as at right.

The patient will feel hot and dry, and will dream in red technicolour. Here is

Pertelote diagnosing for her husband, Chaunticleer:



"No doubt the redness in your dream to-night
Comes from the superfluity and force
Of the red cholera in your blood. Of course.
That is what puts the dreamer in the dread



Of crimsoned arrows, fires flaming red,
 Of great red monsters making as to fight him,
 And big red whelps and little ones to bite him;
 Just so the black and melancholy vapours
 Will set a sleeper shrieking, cutting capers
 And swearing that black bears, black bulls as well,
 Or blackest fiends are hailing him to Hell."

The physician's aim in a case of cholera is to reduce the patient's heat and dryness — at the most propitious astrological moment, of course. In this particular case the practical Pertelote recommends that Chauntecleer should reduce his temperature by eating laxative herbs growing in the garden:

"Pekke hem right up as they grow and ete
 hem yn."

But Chauntecleer scorns this sound practical advice, claims that his dream is a warning of the future sent from on high, and having blinded Pertelote by a multiplicity of similar cases proving his point, administers the coup-de-grâce by quoting at her in Latin with a superior smile on his beak:

"In principio,
 Mulier est hominis confusio.
 Madame, the sentence of th's Latyn is,
 Woman is mannes joye, and al his blis!"

The third and last main point of interest I wish to make does not derive quite so clearly from the Physician's portrait — rather from Chaucer's method in all the portraits. Sometimes Chaucer describes a pilgrim's appearance — his physical characteristics, his dress, the sort of horse he is riding; at others his inward character. And the close relationship between the two, because it is often implied, is often overlooked.

In the Middle Ages, a type of medical treatise was current called the *Physiognomia*; in these *Physiognomies*, the detailed relationship between physical characteristics and inward character was discussed and established. For example, it made a big difference to your temperament whether the wart on your nose was on the tip, the bridge, or on one side or the other. The study of the positions of warts and moles even had a name of its own — METOPOSCOPY.

I have been doing a good deal of work recently on the physiognomical relationship between appearance and character in Chaucer's Pilgrims, and also the effect a way of life can have upon a man's appearance, but I have left myself time for only one example. I have chosen the case of the Summoner because the portrait itself contains some confirmation of my diagnoses. Here are the operative parts of Chaucer's description:

"A Somonour was ther with us in that place,
 That hadde a fyr-reed cherubynnes face,
 For saucefleem he was, with eyen narwe.
 As hoot he was and lecherous as a sparwe,
 With scalled browes blake and piled berd.
 Of his visage children were aferd.
 Ther nas quyk-silver, lytarge, ne brymstoon,
 Boras, ceruce, ne oille of tartre noon;
 Ne oynement that wolde clense and byte,
 That hym mighte helpen of his whelkes white,
 Nor of the knobbes sittynge on his chekes.
 We loved he garleek, oynons, and eek lekes,
 And for to drynken strong wyn, reed as blood;"

"With hym ther rood a gentil PARDONER
 Of Rouncivale, his freend and his compeer,
 That streight was comen fro the court of Rome
 Ful loude he soong 'Com hider, love, to me!'
 Th's Somonour bar to hym a stif burdoun;"

The Summoner suffered originally from GUTTA ROSACEA, as quotations from contemporary medical authorities clearly prove. Andrew Boorde writes:

"*Gutta rosacea* are the Latin words that designate this malady; in English it is called "a sauce fleume face," and the symptoms of it are a redness about the nose and cheeks together with small pimples; it is a privy sign of leprosy... This infection comes of evil diet, and a hot liver, and the disordering of a man's complexion in his youth, of late drink and great surfeiting."

Says Bernardus de Gordon:

"The infallible signs are these: A falling out and scabbiness of the eyebrows, a roundness (rotunditas) of the eyes, and an enlargement of the nostrils externally and a contraction internally. Breathing becomes difficult, and the patient speaks as if through the nose; on the face there is a kind of pallor verging upon the deathly, and the appearance of the face is terrible with its fixed look... The secret signs in the beginning are these: the

color of the face is reddish inclining to blackness, the breathing begins to alter, and the voice becomes hoarse." Bartholomaeus de Glanvilla agrees: "In those afflicted with leprosy the flesh is perceptibly corrupted, the eyes and eyelids are corrugated or wrinkled (*corrugantur*) and have a certain glitter; the nostrils are constricted; and the voice becomes raucous."

Even the Summoner's hoarse-voiced singing is not omitted in Chaucer's careful catalogue of his symptoms; and even the apparent narrowness of his eyes is seen to be caused by the swelling of the eyelids.

There can be no doubt that the Summoner is suffering from alopecia. The small pimples which once indicated *gutta rosacea* have developed into the great matter-infested pustules — "knobbes" and "whekes whyte" — of true leprosy. His eyebrows have fallen out, and his beard is exceedingly thin. His eyes are red and swollen, the lashes have gone, and he can see only through slits. And his hoarse singing indicates the rough and husky voice of the confirmed leper. Small wonder that little children were afraid of him!

But Chaucer has gone farther than the mere symptoms of the disease: he has clearly told us three of the causes, all well-substantiated by contemporary medical authorities. First, association with unclean women: the Summoner is as lecherous as a sparrow. Secondly, strong red wine; the Summoner is frequently drunk. Thirdly, too great a fondness for onions — the Summoner loved onions, garlic and leeks. Finally, Chaucer has given us a list of the recognised treatments.

"Ther nas quy silver. lytarge, ne brymstoon,
Boras, ceruce, ne oille of tartre noon;
Ne oynement that wolde clense and byte."

Curry writes, in *Chaucer and the Mediaeval Sciences*:

"Lanfrank's prescription for the cure of *gutta rosacea* includes 'litargiri, aur:pigmenti, sulphuris viui, viridis eris, oleum tartarinum, argenty viui', and Guy de Chauliac would treat the same disease with 'aigre de citron, ceruse, argent vif, borax, soulfhre et alun, avec huil de tartre'. For the more violent cases of skin disorders and for leprosy, Guy recommends the careful and judicious use of 'le medicament corrosif' or perhaps of 'le medicament caustique', the chief ingredient of which is arsenic — and to which Chaucer clearly refers when he speaks of the 'oynement that wolde clense and bite'."

I have examined, all too briefly for my satisfaction, though doubtless much too tediously for yours, three aspects of the mediaeval medicine — the dependence on astronomy, the doctrine of the humours, and the physiognomia. There is one overriding consideration that I would like to leave with you. The man in whose works we have studied them, Chaucer, was not a doctor, nor even a scientist, but a poet. He knew a good deal of science, of course, rather more than the average educated man of his day. But he used this knowledge as a means to a literary end and not as a scientific end in itself. He did not in fact *find* the Wife of Bath under the joint influence of Venus and Mars; he put her there, so that her subsequent amorousness and aggressiveness would find increased credibility in the eyes of his audience. Scientific knowledge is thus employed to strengthen the credibility of literary characteristics. And this is why — because we have been dealing all evening with a medical science that was still primarily literature — this is why I am particularly happy to lay the small tribute of this lecture up on the altar of medico-literary co-operation.

PREMATURE LABOUR AND BIRTH WEIGHT

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In recent years, various papers, including those of Whitbourne (1930), Piatel and Vandergoten (1940), Salber and Bradshaw (1951a), Scotland (1956) and Hollingsworth (1960), have referred to the birth weight of the African new-born child. They are all in agreement that the birth weight of these infants is lower than that given for European and North African ones.

The ultimate cause of a reduced birth weight is either a deficient growth of the foetus during gestation or an unduly high incidence of labours before term, or, indeed, a combination of both. The third report of the Expert Committee on Maternal and Child Health (1961) supported the view that a preponderance of small babies born to a group of women from an unfavourable environment is more likely to be associated with a deficient growth of the foetus at all stages of gestation.

The present is a study of birth weights in relation to duration of pregnancy amongst Sudanese women. In it, it will be shown that, whereas each of the two factors basically responsible for a reduced birth weight undoubtedly played a part, the explanation for the smallness of the Sudanese infant lies mainly in an unusually high incidence of labours before term.

Material and Method

Case records dating backwards from May, 1963, were examined with the object of collecting 4,000 deliveries where both the length of gestation to the nearest week and the weight of the infant were known. Only pregnancies at and beyond the 28th week were considered. As at the time of compilation no organised Records' Office existed and because a number of records were missing or contained insufficient data, the series was purposely a random one and extended over a period of

six years. The group of patients analysed consisted entirely of Northern as opposed to Southern Sudanese. Ethnologically, these people are a joint product of Hamites (a branch of the Caucasian race) and Negro, with a very strong Arab admixture occurring later. All the patients were delivered at Khartoum Civil Hospital, which is the teaching hospital, and almost all belonged to the poorest non-paying third class wards.

Of the 4,000 pregnancies, 168 were multiple (162 twins and 6 triplets). This high percentage of multiple pregnancies is probably explained by a tendency for these to be delivered in hospital. Of the remaining 3,832 singletons, 248 were still-born. Multiple and still-births were excluded and only the remaining 3,584 single live births were studied. These consisted of 1,902 males and 1,682 females.

The period of gestation was calculated from the first day of the last menstrual period, in many cases corroborated by examination in early pregnancy and, in all cases, by obstetric examination during labour.

Data

The overall mean birth weight amongst the 3,584 live singletons was found to be 6.65 pounds. The weights ranged from 1.19 pounds to 10.75 pounds, male infants being heavier at all stages of gestation (*Table I*). The overall mean birth weight was 6.80 pounds for males and 6.47 pounds for females and at the 40-41 weeks, it was 7.40 pounds per males and 7.15 pounds for females (*Table I*). This table is given in two-weekly intervals so as to minimise any error arising from preference for any particular week or from uncertainty regarding menstruation dates.

Conforming with the recommendations of the Expert Group on Prematurity

TABLE I
Distribution of Single Live Births by Duration of Gestation and Birth Weight

Duration in weeks	MALES		FEMALES	
	Number	Mean Weight (pounds)	Number	Mean Weight (pounds)
28 — 29	32	2.58	48	2.47
30 — 31	58	3.37	50	3.17
32 — 33	70	4.03	68	3.97
34 — 35	134	5.60	124	5.23
36 — 37	224	6.66	168	6.44
38 — 39	610	7.19	540	6.88
40 — 41	738	7.40	650	7.16
42 — 43	36	7.62	34	7.49
Total	1902	6.80	1682	6.47
Number of births (live)	= 3584			
Mean birth weight	= 6.65		pounds	
Error of mean	= 0.09		„	
Standard deviation	= 1.87		„	

under the W.H.O. (1950b), the infants were recorded as premature when their weight was 5.5 pounds (2,500 Gm.) or under. There were 626 live premature infants: 274 males and 352 females, giving an incidence of 17.5 per cent. *Table II* (also set in bi-weekly intervals for reasons already stated) shows the incidence of premature infants at the various stages of gestation. *Table III* shows the distribution of all singletons by weight. It is recorded in one-pound brackets from 2.5

pounds, thus permitting the number of prematures to be seen easily.

For the purpose of this study, the expression "premature labour" has been taken to imply the interruption of pregnancy after the end of the 27th week and before the beginning of the 38th week (*vide infra*). The number of deliveries taking place within this period totalled 967, an incidence of 27.2 per cent (*Table IV*).

Discussion

The mean birth weight of the Sudanese new-born as found in the current study, whilst comparing quite favourably with that of other African infants (*Table V*), does further confirm the smallness of the latter when contrasted with the English or North American ones (*Table VI*). That the smallness of the African baby is not altogether a racial characteristic has been proved by Bakwin and Patrick (1944), who demonstrated, by means of well controlled investigations, that the Negro infant of well-nourished mothers in the higher income bracket showed no significant variation in weight when compared with those born to white women of the same socio-economic stratum.

TABLE II
Distribution of
"Premature Single Live Births"
by Duration of Gestation

Duration in weeks	Total Births	Premature Infants	Percentage
28 — 29	80	80	100.0
30 — 31	108	108	100.0
32 — 33	138	136	98.5
34 — 35	258	166	64.3
36 — 37	392	46	11.7
38 — 39	1150	64	5.6
40 — 41	1388	26	1.9
42 — 43	70	0	0.0
Total	3584	626	17.5

TABLE III
Distribution of live Singletons by Birth Weight

<i>Birth Weight</i> <i>(pounds)</i>		<i>Males</i>	<i>Females</i>	<i>Total</i>
	Up to 2.50	16	28	44
Over	2.50 to 3.50	82	82	164
"	3.50 to 4.50	40	56	96
"	4.50 to 5.50	136	186	322
"	5.50 to 6.50	134	136	270
"	6.50 to 7.50	1150	1040	2190
"	7.50 to 8.50	304	144	448
"	8.50 to 9.50	22	10	32
"	9.50 to 10.50	16	0	16
"	10.50 to 11.50	2	0	2
Total		1902	1682	3584

TABLE IV
Distribution of Single Live Births
by Length of Gestation

<i>Duration of</i> <i>Gestation</i> <i>in weeks</i>	<i>Number</i>	<i>Cumulative</i> <i>Percentage</i>
28 — 29	80	2.2
30 — 31	108	5.2
32 — 33	138	9.1
34 — 35	258	16.3
36 — 37	392	27.2
38 — 39	1150	59.3
40 — 41	1388	98.0
42 — 43	70	100.0
Total	3584	100.0

As already pointed out, the ultimate cause of a reduced birth weight is either (a) a deficient growth of the foetus during gestation, (b) an unduly high incidence of premature labour or (c) a combination of both. That in the Sudanese series a major factor is not a deficient growth during pregnancy is demonstrated by *Table VII*. This table sets out the growth of the foetus at the various stages of pregnancy, a comparison, at the same time, being drawn between the Birmingham (McKeown and Gibson, 1951) and the current series. A remarkable parallelism of growth between the two series is demonstrated. Furthermore, the mean discrepancy of

TABLE V
Mean Birth Weight of Sudanese Infants born after the 28th week
compared with those from other African Countries

<i>Source</i>	<i>Mean Birth Weight</i>	<i>Author</i>
Lagos, Nigeria	6.82	Whitbourne (1930)
Mayombe, Belgian Congo	6.44	Platel & Vandergoten (1940)
Rural Nyasaland	6.56	Platt (1947)
Ibadan, Nigeria	6.31	Walker (1950)
South Africa	{ Europeans	7.47
	{ Coloured	6.85
	{ Bantu	6.77
	{ Indians	6.46
Southern Nigeria	6.62	Bruce-Chwatt (1953)
Kampala, Uganda	{ Bantu	6.44
	{ Non-Bantu	6.38
Vom, Northern Nigeria	6.25	Scotland (1956)
Accra, Ghana	{ Poor Africans	6.31
	{ Rich Africans	7.00
	{ European Expat.	7.12
Ilesha, Western Nigeria	6.17	Gardner & Gardner (1958)
Khartoum, Sudan	6.65	Hollingsworth (1960)
		Morley & Knox (1960)
		Present Series

TABLE VI
Mean Birth Weight of Sudanese Infants born after the 28th week
compared with English and American ones

<i>Nationality</i>	<i>Source</i>	<i>Mean Birth Weight (lbs.)</i>	<i>Author</i>
English	London	7.22	Martin (1931)
English	London	7.22	Huggett (1944-45)
English	Birmingham	7.17	McKeown & Gibson (1951)
American (white)	Cincinnati	7.25	Anderson, Brown & Lyon (1943)
American (negro)		6.81	
American (white)	Atlanta	7.56	Bivings (1934)
American (negro)		6.87	
American (white)	Baltimore	7.13	Taback (1951)
American (negro)		6.63	
Sudanese	Khartoum	6.65	Present series

weight at the various weeks of pregnancy is only 0.06 pounds in favour of the Birmingham baby. This weekly mean variation is disproportionately small; one of a higher magnitude would be expected if an overall mean birth weight disparity of 0.51 pounds (Birmingham, 7.16 pounds; Khartoum, 6.65 pounds) were explainable primarily on the basis of a diminished growth of the foetus *in utero*. Could, therefore, a

high incidence of premature labour have been responsible for the reduced birth weight of this series?

Premature labour is sometimes defined as one which leads to the birth of a premature infant, i.e. one of a weight of 5.5 pounds or less. Such a definition does nothing to establish a relationship between a given point in pregnancy and its corresponding mean birth weight. This is because birth weight in itself is not of necessity an index of the time spent by the foetus *in utero*. Such a definition, too, would exclude, on the one hand, the large baby (e.g. that of the diabetic mother) delivered at the 35th-36th week and, on the other hand, include others who, because of foetal, placental or maternal abnormality are small (< 5.5 pounds) though born at or near term. Regardful of this, a more satisfactory interpretation of premature labour would be based, therefore, on the juncture in pregnancy at which the infant was born. Thus the term "premature labour" has been taken to signify the discontinuation of pregnancy after the end of the 38th week, after Greenhill (1955). This is not an unassailable definition either, if only because it is so dependent on memory and hence inherently open to inaccuracy. Still, the only practical way, as yet, available for assessing the expected date of delivery is based on Naegele's rule of subtracting 3 months from the last menstruation and adding 7 days. Unfortunately, and indeed oddly enough, remembering the date of the last period does not seem to come naturally to most women

TABLE VII
Mean Birth Weight (Males and Females)
related to length of gestation

<i>Length of Gestation in weeks</i>	<i>Mean Birth Weight in pounds</i>	
	<i>Birmingham Hospital Series (1951)</i>	<i>Khartoum Hospital Series</i>
28	2.85	2.41
29	2.75	2.64
30	2.95	3.03
31	3.55	3.47
32	3.85	3.67
33	4.20	4.23
34	5.20	4.94
35	5.95	5.79
36	6.35	6.42
37	6.45	6.72
38	6.70	6.93
39	7.20	7.10
40	7.40	7.27
41	7.60	7.40
42	7.40	7.56
43	7.65	7.71
Overall mean birth weight	7.16*	6.65

* Deduced from Table XIII (McKeown and Gibson, 1951).

TABLE VIII
Distribution of Live Singletons by Length of Gestation

Duration of gestation in weeks	McKeown and Gibson (1951)		Taback (1951)		Present Series	
	No.	Cumulative Per cent	No.	Cumulative Per cent	No.	Cumulative Per cent
28	13	0.08	29	0.3	44	1.2
29	8	0.1	9	0.4	36	2.2
30	15	0.2	27	0.7	50	3.6
31	33	0.4	6	0.8	58	5.2
32	31	0.6	41	1.2	66	7.1
33	58	1.0	12	1.4	72	9.1
34	102	1.6	66	2.1	124	12.6
35	243	3.1	31	2.4	134	16.3
36	407	5.6	192	4.5	222	22.4
37	736	10.1	98	5.6	170	27.2
38	1440	18.9	277	8.6	412	38.7
39	3343	39.3	154	13.2	738	59.3
40	4725	68.2	7990	97.9	1262	94.5
41	2988	86.5	72	98.6	126	98.0
42	1386	95.0	91	99.6	60	99.7
43	486	97.9	12	99.8	10	100.0
Over 43	338	100.0	21	100.0	0	100.0
Total	16,352		9,128		3,584	

and the African woman presents no exception. Furthermore, many women in the present study calculated their dates on the Muhammedan calendar (Higrija) so that some small errors may have resulted in translating these to the Gregorian (Muladija). Nevertheless, there is no prima facie evidence that such errors actually exist in the series. Moreover, it is believed that even if such errors do exist, they will seriously affect the results only if they are gross, frequent and unevenly distributed.

There were 976 labours in this series that, according to the definition accepted above, ended prematurely, constituting 27.2 per cent of all live single deliveries. This is very high incidence and compares very poorly with reports from elsewhere, e.g. McKeown and Gibson (1951) and Taback (1951) viz. 10.1 per cent and 5.6 per cent, respectively (Table VIII). These two series have been selected for comparison because of their large numbers and reliability.

The number of premature infants naturally will be expected to rise with an

increase in labours ending before term. There were 626 such prematures in the current series, an incidence of 17.5 per cent*, which is higher than most other published hospital reports (Table IX). An increased incidence of premature infants, however, is not necessarily a proof of more premature labours. What is more likely to be an index of the incidence of early labours is the number of *unexplained* premature infants. Naturally, the percentage of premature infants of known etiology will increase the more readily one accepts conditions affecting the pregnant woman as being casual rather than incidental to prematurity. Nevertheless, the quoted ratio between explained and unexplained prematures is fairly constant. In the report of neonatal mortality and morbidity by the Joint Committee of Obstetricians and Gynaecologists and the British Paediatric Association (1949), it is

* It is noteworthy that in the Khartoum Civil Hospital Annual Report for 1963/64 (Lumsden and Verzin) the prematurity incidence was 17.8 per cent, thus showing a remarkable constancy.

TABLE IX
Incidence of Premature Infants amongst Singletons

Source	Percentage Incidence	Author
Birmingham, U.K.	5.9	McKeown and Gibson (1951)
Baltimore, U.S.A.		
White	7.4	Taback (1951)
Negro	12.0	
Dublin, Eire	7.2	Feeney (1952)
Southern Rhodesia	5.9	Houghton and Ross (1953)
Natal, South Africa		
Europeans	4.6	Salber (1955) *
Coloured	9.6	
Bantu	11.5	
Indian	18.3	
Accra, Ghana		
Europeans	4.6	Hollingsworth (1960)
Rich Africans	8.6	
Poor Africans	25.1	
Khartoum, Sudan	17.5	Present series

* Salber classified as premature only infants weighing less than 5.5 pounds.

stated that in only 50 per cent of cases can a definite cause for the prematurity be discovered. This figure tallies with observations from other sources, e.g. Aberdeen, 51.9 per cent (Baird, 1945); New York, 50.3 per cent (Bookstaver, 1951); Dublin, 45 per cent (Feeney, 1952); Birmingham, 49.7 per cent (Grosse, 1952); Australia, 43 per cent (Shedden, 1959). Even when these figures are corrected by the exclusion of multiple births, there still exists a considerable discrepancy between them and the 68.7 per cent incidence of *idiopathic* prematurity discovered in the present series. In *Table X*, an attempt has been made to list the main etiological factors which may have precipitated the onset of labour or necessitated the artificial termination of pregnancy.

The high incidence of premature

babies (17.5 per cent), but more especially, the high ratio (430 : 196) of unexplained ones must be regarded as an expression of a high incidence (27.2 per cent) of labours terminating by the 37th week of pregnancy. It is considered, therefore, that in the current series amongst Sudanese, early labour is more closely related to the small birth weight than is a deficient growth of the foetus *in utero*.

Among factors which may have accounted for the large number of premature labours, two appear to be worth mentioning here. They are *malnutrition* and *fatigue*.

Malnutrition

Marked nutritional deprivation was not a feature of the Khartoum series.

TABLE X
Alleged causes of Premature Single Live Births

Cause	Number	Per cent	
Pre-eclamptic Toxaemia	112	17.9	}
A.P.H. (excluding toxaemic separation of placenta)	28	4.5	
Pyrexia	25	4.0	
Miscellaneous	31	4.9	
Unknown	430	68.7	
Total	626	100.0	

Undernutrition and anaemia, however, were present to a greater or lesser extent since almost all patients came from poor families. The diet is thus likely to have been inadequate both in quantity and in its protein, mineral and vitamin content. Anaemia (defined as haemoglobin of 60% or less) was certainly prevalent, and, amongst those in whom the haemoglobin level was recorded, the incidence was 19 per cent.

In any society, poverty must be the ultimate limiting factor in the matter of diet. By any western standards, the majority of the patients forming this series would belong to an extremely low socio-economic stratum. Amongst the Sudanese, other factors — social ones — further contribute to dietary insufficiency and poor nutrition in their women. The paramount claim of hospitality at the expense of the family, especially the women and children, the day-to-day family distribution of provision in favour of the men, and the long periods of lactation often lasting for 18-24 months or merging into another pregnancy — all these combine to undermine the woman's health and sap her nutritional status. How diet influences the length of gestation is not clear. It may be that muscular hypertrophy and hyperplasia on which uterine distension ultimately depends in the second half of pregnancy are adversely affected by an inadequate diet in the early months (Jeffcoate, 1955).

Fatigue

Hard physical work and insufficient rest in the later weeks of pregnancy predispose to early labour (Douglas, 1950, Browne and Browne, 1955 and Baird, 1964). Of significance, too, is the fact that this type of parturient often has a large family, is poorly housed and is generally undernourished. In the Sudan, it is customary for pregnant women of the class examined here to work to within a few days of labour, so that this may have decided some of the early labour.

Summary

Documents of 4,000 Sudanese women delivered at Khartoum Civil Hospital were

studied in respect of birth weight and length of gestation.

The mean birth weight was found to be 6.65 pounds among live singletons.

Evidence is put forth suggesting that the main cause of reduced birth weight in this series is a raised incidence of labours before term.

Two factors — malnutrition and fatigue — operative in the Sudan and almost certainly responsible for, at least, some of the early labours are emphasised.

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- ANDERSON, N.A., BROWN, E.W., and LYON, R.A. (1943): *Amer. J. Dis. Child.*, 65, 523.
- BAIRD, D. (1945): *J. Obstet. Gynaec. Brit. Emp.*, 52, 339.
- BAIRD, D. (1964): *J. Pediat.*, 65, 909.
- BAKWIN, H. and PATRICK, JR. T.W. (1944): *J. Pediat.*, 24, 495.
- BIVINGS, L. (1934): *Amer. J. Obstet. Gynec.*, 27, 725.
- BOOKSTAVER, P.I. (1951): *Amer. J. Obstet. Gynec.*, 61, 399.
- BROWNE, F.J. and BROWNE, J.C. Mc. (1955): *Post-Graduate Obstetrics and Gynaecology*, 2nd. edit., Butterworth & Co., Ltd., London, p. 226.
- BRUCE-CHWATT, L.J. (1953): *Ann. trop. Med. Parasit.*, 46, 173.
- CROSSE, V. MARY (1952): *The Premature Baby*, 3rd edit., Churchill, Ltd., London.
- DOUGLAS, J.W.B. (1950): *J. Obstet. Gynaec. Brit. Emp.*, 57, 143.
- FEENEY, J.K. (1952): *Brit. Med. J.*, 2, 223.
- GARDNER, R.F.R. and GARDNER, E.S. (1958): *J. Obstet. Gynaec. Brit. Emp.*, 65, 749.
- GREENHILL, J.P. (1955): *Principles and Practice of Obstetrics*, edit., Saunders Co., Philadelphia & London, p. 175.
- HOLLINGWORTH, M.J. (1960): *West Afr. Med. J.*, 9, 256.
- HOUGHTON, J.W. and ROSS, W. FRASER (1953): *Trans. R. Soc. trop. Med. Hyg.*, 47, 62.
- HUGGETT, A.Sc.G. (1944-5): *Proc. Nutr. Soc.*, 2, 20.
- JEFFCOATE, T.N.A. (1955): *British Obstetric and Gynaecological Practice: "Obstetrics"*, 1st edit., William Heinemann, London, p. 104.
- LUMSDEN, J.W.F. and VERZIN, J.A. (1965): *Khar-*

- toum Civil Hospital Annual Report, 1963-64, p. 27.
- MARTIN, W.J. (1931): Ann. Eugen. London, 4, 327.
- McKEOWN, T. and GIBSON, J.R. (1951): Brit. J. Soc. Med., 5, 98.
- MORLEY, D. and KNOX, G. (1960): J. Obstet. Gynaec. Brit. Emp., 67, 975.
- PLATEL, G. and VANDERGOTEN, Y. (1940): Ann. Soc. belge. Med. trop., 20, 297.
- PLATT, (1947): Quoted by Jelliffe, D.B., Trans. R. Soc. Trop. Med. Hyg., 46, 13, 1952.
- Report of the Joint Committee of the R.C.O.G. and Brit. Pediat. Assoc. (1949): 48.
- SALBER, E.J. (1955): J. trop. Pediat., 1, 54.
- SALBER, E.J. and BRADSHAW, E.S. (1951a): Brit. J. Soc. Med., 5, 113.
- SCOTLAND, W.H.D. (1956): J. Obstet. Gynaec. Brit. Emp., 63, 120.
- SHEDDAN ADAM, G. (1959): J. Obstet. Gynaec. Brit. Emp., 66, 732.
- TABACK, M. (1951): J. Amer. Med. Ass., 146, 901.
- WALKER A.H.C. (1950): Quoted by Jelliffe, D.B., Trans. R. Soc. trop. Med. Hyg., 46, 13, 1952, from personal communication.
- WHITBOURNE, D. (1930): West Afr. Med. J., 4, 39.
- World Health Organisation (1950b): Expert Group on Prematurity, Final Report, Wld. Hlth. Org. Tech. Rep. Ser. 27.
- World Health Organisation (1961): Expert Committee on Maternal and Child Health. Third Report, Wld. Hlth. Org. Tech. Rep. Ser. 217.

PERINATAL MORTALITY NECROPSY FINDINGS, 1957-1966

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This analysis is an attempt to classify perinatal deaths according to the internationally accepted criteria established by Butler and Bonham (1963). It is hoped that it will serve as a base line for further studies.

All the postmortem reports on perinatal deaths carried out at St. Luke's Hospital during the ten year period 1957 to 1966 were reviewed and the primary necropsy finding in each case was established. The primary necropsy finding was considered to be the morbid anatomical lesion that was the least compatible with continued separate existence. The histological material that was available was also examined before a definite conclusion was reached.

As is the practice in Great Britain and America, the term, Perinatal Death, is here used to include stillbirths and death within the first seven days of life. This is to differentiate it from the term "neonatal

death" (which includes all infants who die within the first four weeks of life). Infants born after twenty-eight weeks' gestation with no sign of life after separation from the mother are considered to be stillbirths.

Classification: The number of peripostmortem examinations carried out during this ten year period was 243. Table I shows the distribution of primary necropsy findings both for stillbirths and for early neonates (first week deaths excluding stillbirths).

The terms used in this classification are mostly self-explanatory. Thus, for example, "antepartum death" (no major lesion) implies a *macerated* stillbirth with no macroscopic or microscopic abnormality.. "Intrapartum anoxia" refers to *fresh* stillbirths or neonates with no major lesion to account for death except signs of intrapartum asphyxia, such as, petechial haemorrhages and congestion of organs, with or without meconium aspiration.

TABLE I

PRIMARY NECROPSY FINDINGS	ST. LUKE'S HOSPITAL SERIES				BUTLER & BONHAM	
	Stillbirths	Early Neonatal Deaths	Perinatal Deaths		Perinatal Deaths	
Congenital Malformation	9	28	37	15.2%	88	16.6%
Isoimmunisation	0	4	4	1.7%	24	4.5%
Antepartum death.						
No major lesion	1	0	1	0.4%	64	12.1%
Antepartum Anoxia	17	0	17	7.0%	56	10.0%
Intrapartum Anoxia	24	58	82	33.7%	120	22.7%
Intrapartum Anoxia and Cerebral Birth Trauma	7	19	26	10.7%	42	8.0%
Cerebral Birth Trauma	4	19	23	9.5%	13	2.5%
Pulmonary Infection	0	22	22	9.1%	27	5.1%
Hyaline Membrane	0	2	2	0.8%	33	6.2%
Massive Pulmonary Haemorrhage	0	2	2	0.8%	13	2.5%
Intraventricular Haemorrhage	1	8	9	3.7%	14	2.6%
Extrapulmonary Infection	0	2	2	0.8%	0	0%
Intrapartum Death.						
No major lesion	0	0	0	0%	9	1.7%
Neonatal Death.						
Histology not available	0	8	8	3.3%	3	0.6%
Miscellaneous	2	4	6	2.5%	5	0.5%
Neonatal Death.						
No pathological findings	0	2	2	0.8%	18	3.4%
Total	65	178	243	100.0%	529	100.0%

In many instances, besides clear evidence of anoxia, there is also some subdural haemorrhage associated with laceration of the falx or tentorium. In these cases it is difficult to decide whether death was due to birth trauma or to anoxia; for this reason such cases are classified under the heading of "Intrapartum anoxia with cerebral birth trauma". The term "Miscellaneous" covers pathological rarities which cannot be included in any of the other categories; examples are Meconium peritonitis, Foetal exsanguination and Adrenal haemorrhage.

Congenital abnormalities: These accounted for 15.2% of all deaths. This figure does not include minor malformations such as a cleft palate or an extra digit. Only abnormalities which appeared to be incompatible with life were included in this category. Even anomalies such as a small septal defect were not considered to be the primary necropsy finding in the presence of a more serious pathological

lesion such as an intraventricular haemorrhage.

TABLE II

System	Single System Involved	Multiple Systems Involved	Total: Each System
Cardiovascular	10	6	16
Alimentary	7	4	11
Urinogenital	6	4	10
Skeletal	1	5	6
Central Nervous	2	3	5
Other	1	1	2

Table II shows the types of malformations which were encountered. In 27 infants there were malformations limited to a single system whereas in 10 infants the malformations involved multiple systems. Congenital malformations were commonest in the Cardiovascular System (16), the Alimentary system (11) and the Urinogenital system (10).

Twelve of the sixteen Cardiovascular malformations presented as single lesions.

These included five Ventricular septal defects, four Atrial septal defects, one Coarctation of the Aorta and one Truncus communis. The other four Cardiovascular malformations presented multiple heart lesions.

Out of ten urinogenital malformations, six showed renal agenesis and two of these were associated with anomalies of the genital organs; there were three cases of Polycystic kidneys and one case of bilateral hydronephrosis.

Among the eleven gastro-intestinal malformations, there were five diaphragmatic hernias, two oesophageal atresias and one rectal stenosis with agenesis of the gall bladder and bile ducts.

Total perinatal deaths in Maltese Islands: in order to ascertain what proportion of perinatal deaths are being subjected to a postmortem examination, we obtained the figures for total stillbirth and perinatal deaths which occurred in Malta during the period 1957 to 1966.

TABLE III

Year	Total Perinatal Deaths	Necropsies Performed	
		No.	%
1957	349	18	5.1
1958	350	20	5.7
1959	344	17	4.9
1960	334	11	3.3
1961	290	14	4.8
1962	316	39	12.3
1963	282	36	12.4
1964	242	18	7.4
1965	201	25	12.4
1966	171	45	26.3
Total	2879	243	8.4

Table III shows that our material only represents 8.4% of all perinatal deaths. It is, however, encouraging to note that in the more recent years there appears to be a trend for the mortality rate to decrease and the number of necropsies to increase so that the percentage of post-mortem examinations being carried out is definitely increasing.

Discussion

Comparison of our necropsy findings

with those of Butler and Bonham show considerable variations. Although, in both series, the commonest cause, of death is Intrapartum anoxia, with Congenital malformations as the second commonest cause, the percentages in many of the categories differ quite markedly. To a very large extent, this can be explained by the fact that whereas in the series of Butler and Bonham, out of a total of 529 perinatal necropsies, there were 348 stillbirths and 181 early neonates, in our own series the proportion is completely reversed. Other divergent findings such as our higher incidence of Intrapartum anoxia and Cerebral birth trauma may be explained by the assumption of the availability of more advanced antenatal and midwifery services in the United Kingdom. Baird *et al.* (1935) showed that the perinatal mortality rate in Aberdeen was reduced to half its previous level and they attributed this, in great part, to the application of the best possible maternity and labour care. The W.H.O. figures for 1962 show that Malta has the second highest perinatal mortality rate in Europe, the figure for Malta being 42.1 per 1,000 live births whereas that for the United Kingdom is 31.4 per 1,000 live births. It must also be noted that whereas, in the series of Butler and Bonham, full histological examination of the lungs was carried out in 87% of all cases, this was only performed in 21% of our own cases. It may, therefore, follow that some of the deaths which we have included in the category of Intrapartum anoxia might have shown Hyaline membrane disease had more frequent histological examination of the lungs been carried out.

Summary

The 243 perinatal postmortem examinations carried out at St. Luke's Hospital during the ten year period 1957-1966 are analysed and classified according to the International classification introduced by Butler and Bonham. Our series is compared with that of Butler and Bonham and explanations are offered for some of the divergent findings. Congenital malformations which accounted for 15.2% of all perinatal deaths, are analysed in some de-

tail. Finally, figures are given to show that in the more recent years, the number of perinatal deaths has decreased whereas the number of necropses has increased.

Acknowledgement

We wish to thank Professor G. P. Xuereb, Head of the Department of Patho-

logy, for his encouragement and helpful criticism.

References

- BUTLER, N.R. and BONHAM, D.G., Perinatal Mortality, (E. & S. Livingstone, Ltd., 1963).
 BAIRD, *et al.* (1953), *J. Obstet. Gynaec. Brit. Emp.*, 81, 473.
 U.N. Demographic Year Book 1963.

THE ORAL CONDITION OF ELDERLY INSTITUTIONALISED MALES

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A survey was carried out in the summer of 1966 of the oral condition of all male patients over 60 years old, at Saint Vincent de Paul Hospital, a government geriatric institution. All the patients were examined by one of us (GEC) with an anglepoise lamp as a light source, except in bedridden patients who were seen under natural light. Dental mirrors and probes were used initially but the dental probe was soon abandoned as many patients objected to its use and tooth probing was not yielding any more information than plain visual examination. The number and condition of the teeth, the presence of calculus and periodontal disease, and the degree of dental attrition were recorded. A questionnaire was completed on the drinking and smoking habits, masticatory ability, dry feeling of oral mucosa and subjective evaluation of dentures, when present.

The patients were classified as non-

smokers, moderate smokers or heavy smokers. It was found, however, that usually the degree of heavy smoking was commensurate with the patient's consumption of alcoholic beverages. Accordingly, the terms adopted were: (a) non-smokers or drinkers; (b) moderate smokers and/or drinkers and (c) heavy smokers and/or drinkers. A moderate smoker and/or drinker was taken to be one who smoked up to 20 cigarettes daily and who consumed less than 1 litre of locally manufactured wine (ten to twelve per cent ethyl alcohol). The heavy drinker and/or smoker surpassed the 1 litre limit as regards wine and smoked more than 20 cigarettes daily.

Information about these habits was initially taken from the patient himself, checked with his clinical records and finally corroborated by a clinical examination (CLG). Thus it was found that the number of cases with chronic bronchitis and emphysema rose steadily from the moderate to the severe groups. Similarly, signs and symptoms of liver cirrhosis with

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ascites, peripheral neuritis and obliterative arterial disease, involving mainly the lower limbs, were prevalent in the heavy drinkers/smokers group.

The majority of the patients examined (over 90 per cent) had been unskilled workers, mostly farm labourers, dock hands and hawkers.

The age distribution of 215 patients examined and a further division into dentulous and edentulous persons are given in Table I.

TABLE I
Age Distribution

	<i>Edentulous</i>	<i>Dentulous</i>	<i>Total</i>
60-64 years	12	18	30
65-69 years	13	19	32
70-74 years	25	29	54
75-79 years	24	25	49
80-84 years	19	14	33
85-89 years	6	10	16
90-94 years	—	1	1
Total	99	116	215

Dentition

Teeth were recorded as Missing; Present; Decayed or Roots. Teeth with an intact crown, including those with early interstitial or fissural caries, severe periodontal disease or gross calculus accretions were classified as PRESENT. Teeth with an obvious large carious cavity were listed as DECAYED; however, since these teeth were usually useful members of the dentition, they have been grouped together

with teeth present in the statistical results. A tooth with complete destruction of the crown and with little or no dental structures above the gingiva was considered as a ROOT.

From the total tooth expectancy of 6880 (215 patients × 32 teeth) there were 1007 (14%) teeth and 284 (4%) roots present. There were 116 (54%) patients with at least one tooth present (Dentulous Group) and the distribution of teeth and roots in this group is given in Table II. The highest number of teeth present was in the 60-64 year group (37%) and the lowest in the 80-84 year group (15%). In the maxilla there were 22% teeth present (ranging from 28% in the 60-64 year group, to 12% in the 80-84 year group) and in the mandible there were 32% teeth present (ranging from 46% in the 60-64 year group to 18% in the 80-84 year group).

The division into a dentulous and an edentulous group tends to give a false picture as several of the patients classified as dentulous had only a few teeth or roots and would in fact have been better off edentulous. Sheldon (1948) adopted the standard of six teeth or more present to consider the natural dentition as adequate. According to this criterion, there were 62 patients with an adequate dentition and 54 with an inadequate natural dentition. Corridan (1965) recently examined a comparable hospitalised group in Cork, Ireland, and his results together with those of a survey carried out in Wolverhampton, England, before the start of the National

TABLE II
Distribution of Teeth and Roots in Dentulous Group

<i>Age Group</i> <i>Years</i>	<i>Tooth Expectancy</i>	<i>Maxilla and Mandible</i>		<i>Maxilla</i>		<i>Mandible</i>	
		<i>Teeth</i>	<i>Roots</i>	<i>Teeth</i>	<i>Roots</i>	<i>Teeth</i>	<i>Roots</i>
60-64	576	212 (37%)	28 (5%)	79 (28%)	17 (6%)	133 (46%)	11 (4%)
65-69	608	182 (28%)	48 (7%)	80 (26%)	15 (4%)	102 (30%)	33 (10%)
70-74	928	267 (28%)	80 (9%)	104 (22%)	37 (8%)	163 (34%)	43 (10%)
75-79	800	210 (25%)	55 (7%)	84 (20%)	25 (6%)	126 (30%)	30 (8%)
80-84	448	67 (15%)	45 (10%)	27 (12%)	22 (10%)	40 (18%)	23 (10%)
85-90	320	68 (20%)	27 (8%)	34 (20%)	13 (8%)	34 (20%)	14 (8%)
90-95	32	I	I			I	I
TOTAL	3712	1007 (27%)	284 (7%)	408 (22%)	129 (6%)	599 (32%)	155 (8%)

Health Service (Sheldon, 1948) on old patients living at home are compared in Table III. The smaller number of edentulous patients in the Maltese group and the larger number of English elderly persons supplied with dentures are the main differences.

Periodontal disease and attrition

An attempt to use a Periodontal Disease Index (Russel 1956) was soon given up. The severe periodontal disease and gross calculus generally present together with the few instances of a good dental arch made indexing superfluous. James's (1960) objective classification of the periodontal status into Good, Moderate and Poor was followed. Such a small number had a moderate gingival condition (none had a good condition) that the periodontal condition of the group is best considered as poor.

The evaluation of the degree of attrition also proved fruitless. Although one did meet the rare individual with even attrition in an adequate dental arch, the majority of dentulous persons had only a few teeth present which occluded irregularly and an evaluation of the degree of attrition was meaningless.

Periodontal disease is the major cause of tooth loss in Malta, in persons over 30 years, (Camilleri, 1966) and it increases in importance in old age. Attention to oral hygiene and treatment of periodontal disease is undoubtedly the chief requirement of the dentulous group.

Mastication

The estimation of masticatory ability was based on the reply given by the patient on whether he was able to eat the crust of Maltese bread or discarded it to

eat the softer central portions only. They were then graded as eating a Hard or Soft diet. In the dentulous patients the Hard/Soft ratio was 57/59 whilst in the edentulous group it was 49/50. There is not much discrepancy between the two groups and probably the presence or otherwise of teeth (as found in our study) does not make much difference to the ability to eat a hard type of diet. It is interesting, however, to note that in the edentulous group who succeeded in wearing their dentures the Hard/Soft ratio was 19/6, suggesting that the persons who persisted in wearing dentures had a better masticatory ability.

Of the triad of complaints of poor aesthetics, local discomfort and limited masticatory function, the latter is the most common and pressing. The possession of a few roots, a mutilated dentition with advanced periodontal disease or a completely edentulous mouth make a major contribution to malnutrition in the elderly (Kemp, 1965).

Prosthetics

There were 99 (46%) totally edentulous patients, of whom 42 had never been fitted with dentures and 57 had been given one or more sets of full upper and full lower dentures. There were also 5 patients who had been supplied with partial dentures and one with a full upper denture. An analysis of the 57 patients who had been supplied with full upper and full lower dentures showed that 25 still wore the dentures whilst 32 had discarded them completely. Of the patients who had been given but did not wear the dentures, 6 appliances had been supplied privately and 26 from the Government Dental Clinic. The successful dentures had been supplied by private practitioners in

TABLE III

	Malta	Cork	Wolverhampton
Own teeth adequate	28.9%	5.1%	8.5%
Own teeth inadequate	25.1%	19.0%	18.1%
Edentulous	46.0%	70.0%	69.0%
(Full upper and lower dentures)	26.6%	24.5%	59.8%
(No natural teeth or dentures)	20.4%	45.5%	9.6%

16 cases and by the Government Dental Clinic in 9 instances. Examination of some of the discarded dentures showed that in many instances the articulation and fit appeared satisfactory. The discrepancy between dentures supplied privately and those supplied by the Government Dental Clinic is best explained by the fact that the former group had been supplied with dentures before they were admitted to the hospital when they were younger and therefore physiologically and psychologically more adaptable to dentures. The dentures fitted in the Government Clinic were often supplied to inmates poorly receptive to dentures. The inability of the aged person to adapt to wearing dentures lies mainly in the neuromuscular mechanism to learn new habits. This has been stressed by dental surgeons (Storer, 1965) and geriatric physicians (Kemp, 1965) alike. In the elderly, a complete dental clearance can seldom be recommended except in cases of gross sepsis (Agate, 1963).

Oral mucosa

The characteristic features of senescent and atrophic oral mucosa such as a glazed red sheen, a diminished elasticity of the cheeks and an indistinct mucocutaneous junction in the lips were commonly seen in our patients. These changes are so subtle and gradual that one can only apply non-specific criteria and record gross alterations only. In our patients, the condition of the oral mucosa was generally good and surprisingly pliant with no overt signs of nutritional deficiencies.

The data on the smoking and drinking habits show that 59 did not smoke or drink alcoholic beverages, 57 were moderate smokers and/or drinkers and 98 heavy smokers and/or drinkers. No data were available on 7 patients.

1. Leukoplakia

A clinical diagnosis of leukoplakia was made when there was a distinct white patch clearly distinguishable from the adjoining normal or atrophic mucosa. Many of the patches, but not all, were slightly raised and involved the cheeks or lips.

There were 16 patients with definite white patches of which 2 suggested the possibility of a premalignant condition. One had a distinct erythematous border and centre (erythroplakia) and the other was a large verrucous lesion lining the whole of both cheeks. Of the 16 patients with leukoplakic patches, 2 were non-smokers/drinkers, one was moderate smoker-drinker, and 13 heavy smokers/drinkers. The accepted relationship between the irritational effect of heavy smoking or drinking and leukoplakia is amply borne out.

2. Pigmentation

Together with the change in the oral mucosa from a bright pink to a more violaceous dull colour seen in nearly all the patients and probably associated with vascular changes, there was in 21 (9.7%) of the patients a distinct dusky brown pigmentation, localised to the cheeks or even affecting the whole of the oral cavity. This was indistinguishable from the pigmentation associated with Addison's disease. Oral pigmentation is often considered a sign of systematic disease, but in fact, it is frequently found in healthy persons and is a common characteristic of the darker races including Caucasian brunettes. Becker (1927) had demonstrated the presence of melanocytes in oral mucosa that showed no clinical evidence of pigmentation. There is a reduction in the number of melanocytes in the skin during senescence (Fitzpatrick *et al.*, 1965) yet Walsh (1964) found that pigmentation increased with age in the skin exposed to the sun. Garn and French (1963) noted that there was no increase in colour depth in the skin which is normally unexposed. The relationship of oral mucosal pigmentation and aging does not seem to have been studied but it is possibly related to local irritation. In the 21 patients with oral pigmentation, 5 were moderate and 16 heavy smokers/drinkers.

3. Other lesions

Other unusual oral lesions encountered were a nodular hyperplasia of the

hard palate and a large haemangioma of the cheek. Four patients had large nodular varicose enlargements of the superficial collecting veins located in the lips and prominent veins in the ventral surface of the tongue were very common.

Comment

The geriatric patient tends to respond to noxious stimuli in an atrophic rather than in a productive manner (Massler, 1956) so that dental and oral symptoms of disease are not prominent. This was so in our survey and very few of the patients had any specific oral complaints. Subjective responses and complaints are generally unreliable so that periodic and systematic examination is essential to recognise early oral disease (Allen, 1963). Recent research in geriatric dentistry has revealed that timely initiation of hormonal, nutritional and vitamin therapy is effective in mitigating or even reversing some of the deteriorative changes occurring in the oral cavity (Muller, 1959). The dental surgeon has an important role in the health team looking after geriatric patients and should keep his patients under constant surveillance rather than wait for specific complaints.

Acknowledgements

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References

- AGATE, J. (1963), *The Practice of Geriatrics*, p. 113. Heinemann, London.
- ALLEN, E.F. in E.V. COWDRY (1963), *The Care of the Geriatric Patient*. 2nd. ed. Chap. 13. C.V. Mosby.
- BECKER, S.W. (1927), *Arch. Dermatol. Syphilol.*, 16, 259.
- CAMILLERI, G.E. (1966), *St. Luke's Hosp. Gaz.* 7, 12.
- CORRIDAN, J.P. (1965) *J. Irish dent. Ass.* 11, 132.
- FITZPATRICK, T.B., SZABO, G. and MITCHELL, R.E. in MONTAGNA, W. (1965), *Aging*. Chap. VII., Pergamon.
- GARN, S.M. and FRENCH, N.Y. (1963), *Am. J. obst. Gynec.* 85, 873.
- JAMES, P.M.C., JACKSON, D., SLACK, G.L. and LAWTON, F.E. (1965), *Arch. oral. Biol.*, 3, 57.
- GEMP, R. (1965), *A new look at Geriatrics*, p. 87, Pitman.
- MASSLER, M. (1956), *N.Y. J. Dent.* 26, 54.
- MULLER, W. (1959) *Zahnaerztl Welt.* 60, 72.
- RUSSEL, A.L. (1965) *J. dent. Res.* 35, 350.
- SHELDON, J.H. (1948), *The social medicine of old age*. Oxford Univ. Press
- WALSH, R.J. (1964), *J. Invest Dermatol.*, 42, 261.

CYSTIC DISEASE OF LUNG —

REPORT OF A CASE TREATED BY LOBECTOMY

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A cyst or cysts of the lung may be a manifestation of disease of a widely varying nature ranging from congenital lobar emphysema to hydatid disease. An exhaustive list of pathological states in which a cystic condition of the lung may be present would also include such conditions as cavitation cancer of the lung, pulmonary tuberculosis and lung abscess. However, the term as used here is limited to a congenital condition of the lung in which a single cyst or multiple cysts are present, scattered throughout the parenchyma of a lung or confined to a lobe or to part of a lobe. Thus bronchogenic cysts of developmental origin but situated outside the substance of the lung, in the para-hilar region or in a fissure would be excluded. Congenital lobar emphysema being considered as developing as a result of an inherent weakness of a lobar bronchus and lacking the appropriate epithelial lining is also excluded.

Lindskog describes the condition as resulting "from error in development of the bronchial buds. Such cysts are typically lined by ciliated mucus-producing epithelium, usually not communicating with the bronchial tree, and having muscle and cartilage within their walls". Occasionally they are found to communicate with the respiratory tract.

Other terms that have been used are: "pulmonary cysts, congenital cystic disease of the lung, pneumocysts, solitary and balloon cysts of the lung". The term "congenital bronchiectasis" is particularly confusing, but true bronchiectasis is said to be occasionally present at birth.

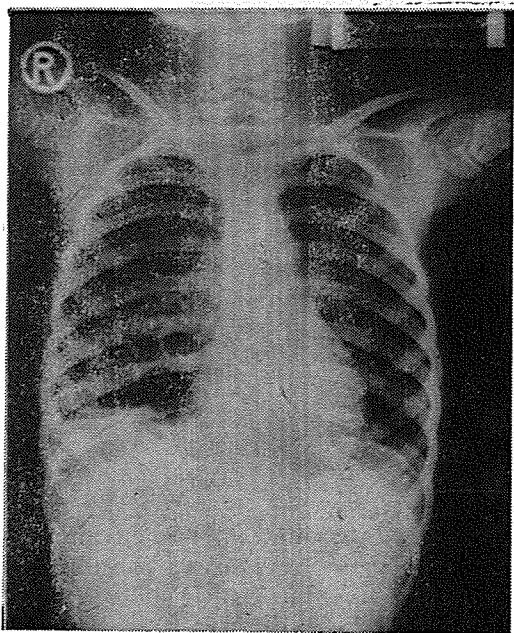
The matter of the lining is an important distinguishing point, but as Lindskog,

Potts and others state, in the event of supervening infection it may be difficult or impossible to make out and to distinguish hence from an abscess of the lung.

The earliest mention of cystic lungs is probably by Thomas Bartholinus in 1687, (Leyden edition of Malpighius). H. Meyer published the first clinical report on this condition in 1859. By 1925 Koontz could collect 108 cases from the literature and add one of his own. In an early paper on Pulmonary Lobectomy by Robert and Nelson in 1933 one of the ten cases described had a pathological diagnosis of "Congenital cystic type of bronchiectasis" with "the lobe showing two large cysts and several small ones, and microscopic section showing that the epithelium was similar to that found in the trachea.

Case Report

A girl aged 4 was referred to St. Luke's Hospital urgently on the 27th December, 1964, for "acute tonsillitis and severe arthralgia of the dorsolumbar spine". She had had a 3-day history of fever, pain in the back and vomiting. On examination she looked flushed and ill, her fauces being intensely injected; her chest was clear. She was put on 1 million units of Penicillin and 0.5 g. of Streptomycin daily. By the 29th she was showing no improvement; her temperature rose to 104 F. She complained of pain in the right hypochondrium and examination of the chest revealed diminished air entry to the right base. Investigations gave the following results: Hgb. 68%; W.B.C. 10,900 (Poly: 65%, Lymph. 20%; Mono: 15%); E.S.R. 40 mm. 1st. hr.; Mantoux and Serum

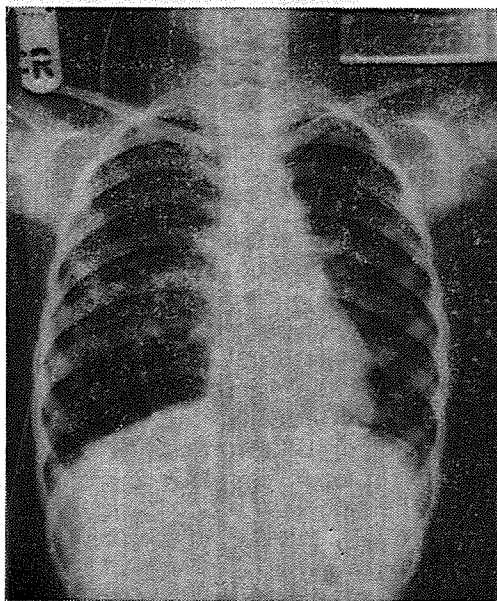


10. 3. 65: Showing cystic changes rt. lower lobe with adjoining areas of consolidation.

agglutination tests: negative. No protein and no casts were found in the urine. Throat and nasal swabs and a stool culture showed no pathogenic organisms. Examination of gastric contents showed no *Myco. tuberculosis* to be present. X-ray examination of the chest showed 3 cavities with fluid levels to be present in the right lung. There was a mottled consolidation of the right hilar region. On 21. 1. 65 the child was put on 750 mgm. chloramphenicol daily, and for the next 5 months she was put on erythromycin or chloramphenicol or penicillin and streptomycin. On the 4th January, 1965, she was given a blood transfusion (150 ml.). A bronchogram was performed on 6. 6. 65, which failed to show any filling of the right, middle and lower lobes.

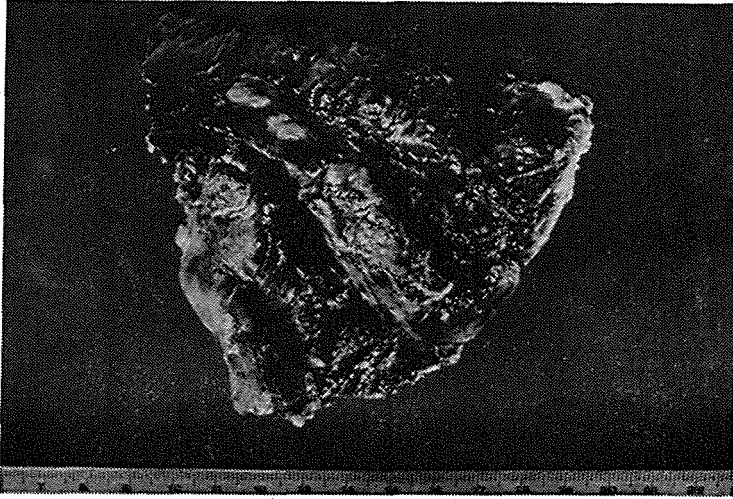
Operation was performed on 3. 8. 65 under general anaesthesia (Dr. C. Podestà). The chest was opened through a right postero-lateral thoracotomy incision along the upper border of the sixth rib. The right lower lobe was found to be partially collapsed and adherent to parietal pleura over its mediastinal and diaphragmatic aspects. These adhesions were dense and vascular and their separation caused fairly severe bleeding, not easily controlled. She was

given 250 ml whole blood and 300 ml plasma over the operation. The right lower lobe was removed and the upper and middle lobes, which appeared normal to sight and palpation, could be made to expand quite readily. The chest was closed with one intrapleural drain. Post-operative progress was satisfactory. The drain was removed on the third day and the sutures on the tenth after operation. Chest X-ray (16. 9. 65) showed some residual pneumothorax. This cleared up slowly with full expansion of the upper and middle lobes.



21. 5. 65: Cysts still evident, the surrounding pneumonitis is less marked.

The Histological Report (Professor G. P. Xuereb) was as follows: Received in formol saline the lower lobe of the right lung measuring $10.4 \times 9.7 \times 5.5$ cm. Part of the lobe is well aerated; its border is distinct. There are however, fibrous, haemorrhagic pleural adhesions over an area of lung 9 cm. from above down and 9 cm. from side to side; the pulmonary tissue at this side is replaced by cystic collapsed tissue. The specimen has been preserved whole. Microscopical examination shows haemorrhage and oedema within alveoli; there are areas of pneumonic consolidation with fibrosis, focal aggregates of lymphocytes, and eosinophilic infiltration. Large mononuclear cells are also present. There is no bronchi-



The excised cystic right lower lobe.

ectatic dilatation. Cystic lobe right lung; haemorrhage and oedema.

Discussion

The true incidence of congenital cystic disease of the lung is difficult to determine. In a recent report on 372 lung resections in children and adolescents from H. Bruegger in Allgau, Germany, the presence of lung cysts or cystlike formations was the indication for operation only in 5 of the cases. In the same series there are 4 cases of congenital pulmonary emphysema. Moersch and Claget (1947) described a series of 44 cases seen over a period of 10 years at the Mayo Clinic. Most authors are in fact agreed that the lesion is a rare one but do not give figures.

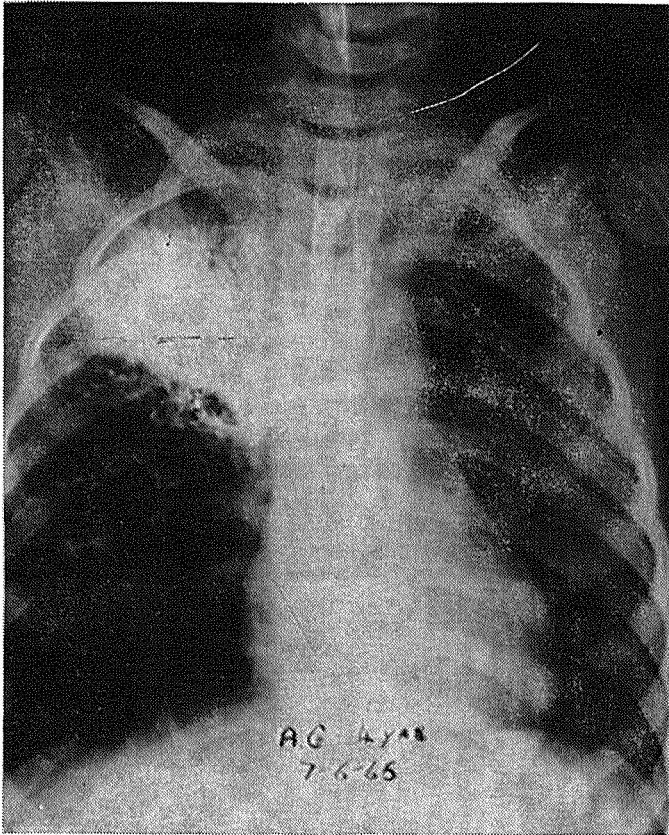
The cysts commonly have a bronchial communication which predisposes them to the development of complications. These are mainly of two kinds. In the first place they may suddenly enlarge as a result of a sharp rise of tension within them and cause acute symptoms from the considerable compression and displacement of surrounding healthy lung and mediastinum. This may happen in very young children and may call for urgent and radical surgery. Gross (1946) describes a case where pneumonectomy was performed with success on a three week infant which developed this type of complication. They may secondly, become acutely infected giving rise to a severe

pulmonary infection. This is the commoner event and occurred in 26 of the 92 cases studied by Lichtenstein (1953). In this latter series no fewer than 30 of the cases were symptomless and discovered on routine investigation.

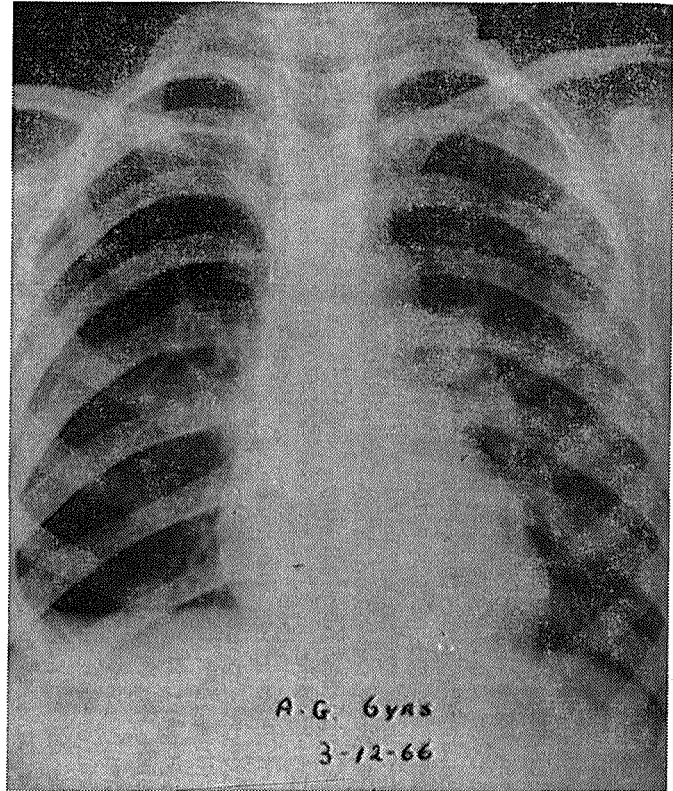
The case reported here presented as a severe pulmonary infection requiring parenteral antibiotic therapy and blood transfusion. Although the brunt of the infection was brought under control in a matter of 12 days it went on smouldering for 8 months until the diseased tissue was removed surgically.

A third group of cases may come to light as a result of investigations prompted by the presence of symptoms in patients who are not actually ill. Haemoptysis is one such symptom. This was present in 16 out of 22 cases studied by Dickson, Clagett and McDonald (1946). Other symptoms are cough and expectoration, pain and soreness of the chest and shortness of breath.

Although pre-operative diagnosis is often possible a definitive diagnosis may have to wait on an examination of resected tissue by the pathologist. The history is often suggestive and clinical examination will focus scrutiny on the region of the lung field involved. It is however on X-ray studies that a diagnosis is based. Plain X-rays in postero-anterior and lateral erect and supine projections will show up the cysts and provide information as to their contents and the presence and degree



Bronchogram — showing absence of filling of right middle and lower lobes.



3. 12. 66: The middle lobe is fully expanded.

of peribronchial inflammation.

Congenital cysts as Flavell (1957) underlines are generally large and more uniform than those seen in congenital bronchiectasis, and the degree of peribronchial inflammation is much less.

In infants and children a real difficulty exists in distinguishing congenital cysts from the alveolar cysts that develop on staphylococcal pneumonia. A thorough search for pathogenic strains of staphylococci from the respiratory and gastrointestinal tracts and from the blood is necessary. In the case reported here all such investigations were negative.

Other points of distinction from secondary staphylococcal pneumatoceles are the rapidity with which they develop often in the late pneumonic phase of the illness, and the quick fluctuations in size they not uncommonly show (Potts and Riker, 1951). The differentiation is important because of the difference in management required for the two conditions; staphylococcal pneumatoceles are often multiple and regress gradually. They may take a year to do so (Swenson, 1959). Other conditions which may have to be differentiated in children are fibrocystic disease of the pancreas, and Letterer-Siwe disease. In adults pulmonary tuberculosis with cyst formation, has to be excluded. In Moersch and Clagett's series six cases were being treated for pulmonary tuberculosis before diagnosis was established.

Pulmonary abscess, empyema, carcinoma and mediastinal tumour have also to be differentiated. Maier and Haight (1940) have underlined the difficulty of differentiating from empyema. Lindskog, Liebow and Glenn (1962) point out that when infection supervenes it may be difficult or impossible to distinguish an infected intraparenchymal cyst from abscess of the lung, and Sellors has written thus: "the treatment of cystic disease of the lung does not make satisfactory reading and the number of cases that have been aspirated or drained without further attempt at cure shows how little the condition is understood."

The treatment of choice is surgical excision of the diseased tissue, the pre-

ferred operation is lobectomy. In infected cases the management rests on appropriate antibiotic therapy coupled with supportive measures to control and contain the pneumonitis followed by bronchoscopy in order accurately to localize the disease, followed by operation. Bronchoscopy is of little value and is not advised. More limited resection is advised by some but is seldom practicable. As eventual infection of the cyst is the rule surgery is mandatory in localised disease however mild the symptoms. This is generally regarded justifiable "in this era of safe thoracotomy".

The bronchogram of the case reported here showed normal filling of the right upper lobe but failed to show proper filling of the middle or lower lobes. At operation the middle lobe was found to be collapsed but expanded readily on removal of the diseased lower lobe. Thus the true extent of the disease may only be determined at operation.

Cysts that enlarge suddenly and cause acute respiratory embarrassment by displacement and compression may require urgent and radical surgery. Simple decompression by aspiration does not work and predisposes to pulmonary infection. It is generally regarded inadvisable. Infants and children stand pulmonary resection well. No adverse effect on growth and development has been noted following pneumonectomy in infants.

Summary

A case of a four year old girl presenting as an acute pulmonary infection and found to have cystic disease of the right lower lobe is here reported. A successful result followed lobectomy.

Some aspects of cystic disease (Congenital) of the lung are discussed.

References

- BURCH, B.H. and MILLER, A.C. (1961) *Surgical Diseases of the lung.*
 DICKSON, J.A., CLAGETT, O.T. and MACDONALD, J.R. (1946), *J. Thor. Surg.*, 15, 196.
 FLAVELL, G. (1957). *An introduction to Chest Surgery.* Oxford University Press.

- FLEMING (1934). Arch. Dis. Child., 9, 201.
 GROSS, R. (1946). Ann. Surg. 123, 229.
 KOONTZ, A.R. (1935). Bull. Johns Hopkins Hosp., 57, 247.
 LICHTENSTEIN, H. (1953). Dis. Chest, 24, 646.
 LINDSKOG, G.E., LIEBOW, A.A. and GLENN, W.W.L. (1962). Thoracic and Cardio-Vascular Surgery with related pathology. Appleton-Century-Crofts.
 MAIER, H.C. and HAIGHT, C. (1940). J. Thor. Surg., 9, 471.
 MILLER, A.C. (1926). Arch. Surg., 12, 392.
 MOERSCH, H.J. and CLAGETT, O.T. (1947). J. Thor. Surg., 16, 179.
 POTTS, W.J. and RIKER, W.L. (1951). Arch. Surg., Surg., 61, 684.
 SELLORS, T.H. (1936). Tub., 20, 49.
 SWENSON, O. (1959). Paediatric Surgery. Staples. Appleton-Century-Crofts.

RHEUMATIC FEVER IN MALTESE CHILDREN

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The incidence of acute rheumatism in Maltese children has not been studied so far. In 1956 Professor J. E. Debono was of the opinion that the disease had become more frequent since the end of the last war. Our impression is that the disease has become even more common.

TABLE I
Showing number of children treated for acute rheumatism in one of the children's wards

1957	2
1958	3
1959	7
1960	6
1961	6
1962	5
1963	11
1964	6
1965	11
1966	13

During the years 1957 to 1966 inclusive 70 children were treated for rheumatic fever at one of the two Children's Wards at St. Luke's Hospital. It is reckoned that a similar number were treated at the other Children's Ward during the same period. At the same time an unknown number of children over 9 years of age were treated in the Medical Wards (since 1966 patients under the age of 12 years

have been admitted to the Children's Wards) and an unknown number were treated at home and in private hospitals. Were all the figures known they would make up a considerable number. Rheumatic fever occurs too frequently to permit complacency. Bland and Jones (1951) in their study of 1000 rheumatic patients followed since childhood found signs of heart disease in 80%. They also concluded that 25% of rheumatic patients die within 30 years of the onset of the illness.

Initial attacks of rheumatic fever and subsequent recurrence are causally related to preceding infection by any type of Group A. haemolytic streptococci. This has now been accepted on clinical, serological, epidemiological and prophylactic evidence. Studies of rheumatic fever in closed communities have shown a fair constant attack rate of 3% following untreated epidemic streptococcal infections.

The symptoms and signs of rheumatic fever vary greatly. The clinical findings are determined by the sites of involvement, the severity of the lesions, the time of appearance during the course of the illness, and the stage at which the patient is first examined (Markowitz and Kuttner 1965). Yet it is very important that the physician be reasonably certain of the diagnosis. Treatment is prolonged

and expensive. The patient is confined to bed for several weeks or months and diagnosis may produce acute or chronic emotional tension in the parents or patient (Baum 1963).

Unfortunately there is no single diagnostic symptom or sign and no specific laboratory test for rheumatic fever. In 1944 the late T. Duckett Jones published criteria to guide the physician in making the diagnosis. These were subsequently revised by the American Heart Association. It is worthwhile repeating them here:

Major Criteria

- Carditis
- Polyarthritis
- Chorea
- Subcutaneous nodules
- Erythema marginatum.

Minor Criteria

- Fever
- Arthralgia
- Prolonged P-R interval in E.C.G.
- Increased E.S.R. or C-reactive protein
- Preceding group A streptococcal infection

Previous rheumatic fever or inactive rheumatic heart disease.

The Co-operative Clinical Trial (1955) of the Medical Research Council and American Heart Association accepted two major manifestations or one major and two minor manifestations as justifying the diagnosis. Difficulties in diagnosis, however, may still occur because of the limitations of Jones's criteria and the great variability of the disease. A mild attack of rheumatic fever or a child presenting with abdominal pain may not satisfy the criteria. One of the commonest sources of difficulty is when the patient presents with polyarthritis, fever and a raised E.S.R. because this group of findings is common to several other diseases. Other manifestations, not included in the criteria, but which provide additional evidence of rheumatic fever are pallor, loss of weight, easy fatigability, erythema nodosum, pre-cordial pain and epistaxis.

During the years 1962 to 1966 inclusive 66 children were referred to the Children's Ward for rheumatic fever. Following a period of observation and investigation

42 children were found to be actually suffering from the disease. Seventeen children were found to have short term fever or non-specific arthritis which cleared up within 3 days of admission. Of the remaining seven patients, two had rheumatoid arthritis, one was found to have an appendix abscess, one had a neuroblastoma with metastases at the lower ends of the femora, one had acute lymphoblastic leukaemia, one had typhoid fever and the remaining one had undulant fever. Two patients were originally referred for fever of unknown origin and two for acute abdominal pain and these were subsequently found to be suffering from rheumatic fever. This made up our total of 46 patients. Thirty seven had an initial attack and 9 had a recurrence.

We have made a study of the 46 children who were treated for rheumatic fever. Rheumatic fever has long been associated with poor living conditions and substandard housing. We have confirmed this. Affected children came mainly from large families, the average number of children in each family being 5.4. The average number of rooms per family was 3.6. Regarding the father's occupations 12 belonged to class V, 8 to class IV, 15 to class III and 3 to class II. The occupations of the remaining 8 fathers had not been recorded. The ages of the patients ranged from 3 to 11 years with an average of 7.3 years. Fourteen of the patients had a previous history of a sore throat or tonsillitis and 2 patients had furunculosis. In those patients who had no such history we assumed that there was a mild or sub-clinical infection.

Four of the children had had their tonsils removed before they had their initial attack of rheumatic fever.

Carditis occurred in 40 of the children. A significant heart murmur was found in 33. X-ray chest for heart was taken of the 22 patients and the heart was enlarged in 14 of them. One child had pericarditis with effusion. Congestive heart failure occurred in 8 patients. Five of the latter had a history of rheumatic fever. Polyarthritis as evidenced by pain and clinical signs involving two or more joints occurred in 28. Chorea affected 5 girls and

one boy. One girl developed hemi-chorea while she was being treated for rheumatic carditis. In three of the children chorea was the sole manifestation of the disease. Subcutaneous nodules were not noted in any of the children but erythema marginatum was observed in one child.

The most common minor manifestation met with was a raised E.S.R. which was found in 41. Fever occurred in 38. Arthralgia was complained of by 4 children who did not have polyarthritis. More frequent use of the electrocardiogram in the Children's Ward has only been possible during the last two years. In all 13 of the patients had an E.C.G. A prolonged P-R interval was found in one patient. This may possibly be due to the fact that the electrocardiograms were taken several days after admission. Of the other manifestations, pallor was almost universal during the acute stage.

Comment

Rheumatic fever can be a very serious and crippling disease. It is evident that the disease is far from rare in Malta and is probably on the increase. In order that the incidence of rheumatic fever and the prevalence of rheumatic heart disease in the Maltese Islands be known the disease should be made notifiable. This has been the practice for some years in selected areas of Great Britain notably Sheffield and Bristol. The criteria for notification being:

1. Rheumatic pains or arthritis accompanied by a rise in temperature.
2. Rheumatic chorea.
3. Rheumatic carditis.
4. Valvular heart disease of rheumatic origin (Jameson and Parkinson 1963). Notification and registration of the disease has also been strongly recommended by the W.H.O. expert committee on Rheumatic Fever 1966 as the first step in any programme directed at the prevention of rheumatic fever. For a start, known cases of rheumatic fever should be notified. The next step would be to detect previously unknown cases through examination of special population groups

such as school children and expectant mothers.

If group A streptococcal infection could be eradicated rheumatic fever would disappear. The prevention of acute rheumatism is possible today only by prevention or treatment of group A streptococcal infections (W.H.O. Report 1966). Initial attacks which might possibly be prevented still occur because many children do not receive medical attention for antecedent streptococcal infection either through ignorance and poverty, or through the misguided advice of neighbours and persons selling medicines over the counter. Unfortunately a popular belief shared by many is that tonsillectomy prevents rheumatic fever but, even in this small series, 4 children developed acute rheumatism in spite of previous tonsillectomy.

The diagnosis of streptococcal pharyngitis or tonsillitis cannot be made unless the physician has access to a bacteriological service which is available every day including Sundays, holidays and festas. Many cases of pharyngitis and tonsillitis — with or without exudate — are non-bacterial in aetiology and do not lead to rheumatic fever. Patients with such infections do not benefit from antibiotic therapy. A culture of the throat would confirm or disprove streptococcal infection. Throat cultures from patients with acute streptococcal infections are positive for Beta-haemolytic streptococci in over 95% of cases (Markowitz and Kuttner 1965).

The drug of choice in the treatment of streptococcal infections is penicillin. As yet no group A streptococcus has been confirmed as penicillin resistant. Unfortunately it often happens that the drug is only given for two or three days until symptoms have ceased to worry the parents. For penicillin to be effective in eliminating the streptococcus it must be given for seven to ten days. An alternative and convenient way has been recommended where crystalline penicillin G., procain penicillin and dibenzyl penicillin 1,200,000 I.U. are given in a single injection. Sulphonamides even though they suppress the symptoms and signs of acute streptococcal tonsillitis have been found

to be ineffective in the prevention of rheumatic fever presumably because they are unable to eliminate the streptococcus from the upper respiratory tract (W.H.O. Report 1966). Broad spectrum antibiotics are less efficient than penicillin and much more expensive. Erythromycin has been recommended for use in those allergic to penicillin.

Recurrent attacks of rheumatic fever in known rheumatic patients can be prevented by continuous prophylactic administration of penicillin, sulphonamides or broad spectrum antibiotics. This prophylactic treatment is also recommended for those patients with inactive rheumatic heart disease and in those with "probable rheumatic Fever" not meeting Jones's criteria, e.g. those with "pure" chorea. In the present state of knowledge prophylactic treatment is recommended for several years. Phenoxymethyl penicillin 100 to 125 mg orally may be given twice daily. When the parents are unreliable it is better to give dibenzyl penicillin 1,200,000 i.u. intramuscularly every 4 weeks to children and every three weeks to adolescents. If sulphonamides are used in prophylaxis sulphadiazine for example, 0.5 G. a day

may be given to children and 1 G. daily to adolescents.

Summary

Rheumatic fever is still one of our great paediatric problems and is probably on the increase. A study of 46 children who had acute rheumatism has been presented. The disease should be made notifiable. Facilities for the isolation of the streptococcus should be made available to all physicians. Rheumatic fever and its recurrences can be prevented by adequate chemotherapy.

References

- BAUM, D. (1963). *Ped. Clin. N. Amer.*, 10, 899.
 BLAND, E.F. and JONES, T.D. (1951). *Circulation*, 4, 836.
 DEBONO, J.E. (1956). 'The Rheumatic Child', A survey of Child Welfare Problems, by the "Save the Children Fund". (Malta, Gov. Muscat).
 JAMESON and PARKINSON (1966). A synopsis of Hygiene, 12th Edition, J & A. Churchill, London.
 MARKOWITZ and KUTTNER (1965). *Rheumatic Fever diagnosis and prevention*. W.B. Saunders, London.
 World Health Organisation (1966). *Prevention of Rheumatic Fever*, Technical Report Series, No. 342. Geneva.

The agent for "Abecedin", made by Napp Classical Ethical Products is Mr. G. Borg-Barthel of 47 South Street, Valletta. In some copies of our last issue another firm was mistakenly given as the agent.

DISEASES COMMON TO MAN AND ANIMALS IN MALTA

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Rather more than one hundred zoonoses are recognised in the world, of which relatively few are likely to be of local interest. It is not proposed here to give a list of them all, or for that matter to attempt to give full details of those relevant to Malta. This type of information is far better found in published text books, two of which are given in the references. The purpose of this article is rather to record some recent developments in our own knowledge of animal diseases which are, or may be, of significance to humans in Malta.

DISEASES KNOWN TO EXIST IN MALTA

Bacterial Diseases

Tuberculosis. The bovine form of this disease is now on the verge of eradication. However, a number of pigs have been found recently with isolated lesions in the sub-maxillary or pharyngeal glands. Work is being done to determine whether these infections are human, bovine or avian in origin. The significance is that flesh from this part of the carcass is commonly used for the manufacture of sausages.

Tetanus in equines is common. It is seen also occasionally in cattle, sheep, goats and pigs.

Anthrax is remarkable in its rarity. Only occasional cases have been diagnosed in cattle. Should the disease occur in sheep and goats, contamination of the grazing areas could well occur and the situation would change quite rapidly.

Brucellosis has been too familiar in Malta to warrant description. However it is perhaps not generally appreciated that a type of chronic brucellosis exists in man in which the patient is negative to the agglutination test, but may show varying degrees of headache, irritability, depression, arthritis and backache. In the ab-

sence of laboratory tests, this type of patient must be easy to confuse with the "neurotic". Kerr *et al* (1966) have shown that a combination of the Complement Fixation Test and the Anti-human Globulin test will demonstrate significant levels of antibody in such cases.

Salmonellosis. *S. typhi murium* is known to affect most forms of livestock. In Malta it has so far been encountered only in pigeons and rabbits. In sheep the infection is often fatal; two or three sudden deaths occur and then the outbreak ceases. The danger here is that outbreaks may well pass unreported and undiagnosed and that shepherds may "salvage" animals in the early stages of septicaemia, (Crowther, R.W., 1957). Ducks are a potential hazard; but this possibility applies more to other countries where they have the opportunity to consume mud from the bottom of ponds open to contamination. Cases of *S. cholerae suis* have been found in pigs, but this micro-organism is not recognised as a human pathogen.

Erysipelas is endemic amongst pigs in Malta and it is quite common in the abattoir to see obviously infected carcasses awaiting inspection. Despite this, however, localised infections amongst the butchers handling these carcasses seem to be comparatively rare. Possibly, if one were not familiar with the rather characteristic erythema, this type of infected wound might pass unrecognised, and would in any case yield to standard antibi-
otical treatment.

Listeria infections in man occur usually as a meningo-encephalitis, as a septicaemia of infants, or as a cause of habitual abortions. A number of other manifestations are known and it is becoming increasingly clear that the infection is more common than it was once thought to be. In Malta a case of fatal septicaemia was seen recently in an adult pig. The animal came from stock imported

two years ago which had been distributed to several farms. On two of these farms stillbirths and weak piglets had been reported from the same parent stock about two months previously. At the time these were attributed to vitamin A deficiency.

L. monocytogenes is known to attack a large number of mammals and many birds and has a wide distribution. It is unlikely that this case represents the first introduction of the disease into Malta. An excellent review of *Listeria* infections was published by Gray and Killinger (1966).

Clostridial infections. Enterotoxaemia due to *Cl. welchii* has been seen locally in goats and in rabbits. It could also occur in sheep, pigs and cattle. The potential hazard here is that livestock passing large numbers of clostridia in their faeces are contaminating their surroundings with gangrene producing organisms. In sheep, multiple gangrene infections following needle puncture have been observed after mass vaccination campaigns.

Staphylococcal food poisoning. Staphylococcal mastitis is recognised in Malta amongst cattle, sheep and goats and food poisoning from raw milk used to be fairly common in the days before pasteurisation. It is rarely seen now, though occasional cases occur when cream in pastries is contaminated by human carriers. In some Mediterranean countries cheese poisoning is quite common. The type of cheese affected is similar in appearance to a Gruyère and during its manufacture the milk is held for several hours at around blood temperature. Any pathogenic staphylococci present are thus given an opportunity to multiply and to produce a heat stable enterotoxin which remains thereafter in the cheese.

Leishmaniasis. Cachia and Fenech (1964) present a review of Kala-Azar in Malta in which it is shown that the incidence of human cases has fallen sharply from an annual figure of around 200 cases in 1948 to a level of 25 or less since 1955. They credit this reduction to improvements in rural health, sanitation and hygiene, to the use of insecticide sprays to control the sand-fly population and to

the control of stray dogs. In 1949, 8 out of 718 spleens of stray dogs were found to contain Leishman-Donovan bodies. (Medical & Health Department Annual Report 1949). This in itself was an improvement on the figures for 1911 when 7 out of 53 stray dogs were found to be positive. The incidence in dogs now is probably lower than the 1% reported in 1949.

Leptospirosis in man due to *L. ichterohaemorrhagiae* occurs occasionally in Malta and rats are usually incriminated as the source of infection. Acute clinical cases of Leptospirosis in dogs are uncommon and it does not seem that they are often a source of infection to humans.

Fungal Diseases

In volume one of this journal Fenech and Grixti describe a case of pulmonary moniliasis in a poultry farmer. Moniliasis of the crop is recognised in birds, as is also aspergillosis of the respiratory tract. Probably anyone working near stocks of mouldy forage is at the risk of this type of infection.

In the U.K. certain forms of pulmonary oedema in cattle are believed to be associated with an anaphylactic reaction to certain moulds, principally the Actinomycetes. A similar condition is recognised in the farmers themselves, (Omar and Kirch, 1966).

Parasitic Diseases

Cys. cellulosa and *Cys. saginata* are very seldom encountered during meat inspection. Hydatid cysts are uncommon and *Trichinella spiralis* has not been seen for many years. This situation exists despite the lack of hygiene on many of our farms and can be attributed only to the fact that practically the whole of our local meat is subject to inspection. In other countries where sheep and goats are frequently slaughtered in villages and where the discarded offal is normally thrown to stray dogs, hydatid infections in humans can pose a serious problem.

DISEASES OF UNCERTAIN SIGNIFICANCE IN MALTA

Viral Diseases

Psittacosis. No case of this disease has yet been diagnosed in parrots or in any avian species. However, wild parrots and other members of the same family are frequently brought in from abroad and these are more dangerous than the average pet parrot brought here which has been kept in comparative isolation for some time before arrival. Unexplained cases of pulmonary disease amongst persons handling such birds would be suspicious.

Q. Fever has not been recognised amongst livestock in Malta; but since it does not produce symptoms in animals, this is hardly surprising. The disease is endemic throughout the world. Infected goats, sheep and cattle do not abort but will pass enormous numbers of virus particles at the time of parturition. An influenza-like infection in a shepherd during the lambing or kidding season would be suspicious.

Cat Scratch Fever is not very well understood. It is believed to be caused by a virus which subsists benignly in cats; but which produces in humans a local inflammatory reaction and a mild fever.

Milkers' infections. Ulcerative conditions of the teats and udders of cattle may be due to Cow Pox (*Vaccinia*), or to one of the Para-vaccinia or the Herpes groups of viruses. The condition in man known as "milker's nodule" or Pseudo Cow Pox is at present accepted as falling in the Para-vaccinia group (Peters *et al.* 1964 and Naginton *et al.* 1965). This group also includes the virus of Contagious Pustular Dermatitis (C.P.D.) which may attack sheep, goats and man. Both Cow Pox and Pseudo Cow Pox have been recognised as zoonoses since the time of Jenner; but the isolation of Herpes viruses from cattle by Martin *et al.* (1966) and others is more recent and their significance to humans is not quite certain. For that matter, we do not know how dangerous human cases are to cattle. In Malta, C.P.D. infections are recognised in sheep and goats, but from past experience it

would seem that human infections rarely, if ever, occur from this source.

Herpes virus Simiae or *Virus B.* has not yet been recognised in monkeys imported into Malta. Humans are usually infected when bitten by monkeys, following which vesicles are formed at the site, followed by lymphadenitis and meningo-encephalitis. In monkeys the disease appears often to be much less severe. Hartley (1964) reports finding 30 infected monkeys out of two consignments totalling 300. Of these, however, only one showed visible ulcerations. Probably wild monkeys, purchased for research purposes or for zoos, are more dangerous than those which have been kept as pets for some time in relative isolation from their own kind. However, it is worth remembering that monkeys are imported into Malta fairly frequently and could carry this virus without showing obvious symptoms or lesions.

Protozoal Infections

Relapsing Fever was recognised in Cyprus during the last war by Gambles and Coghill (1948). The parasite was transferred from small mammals to humans by Argasid ticks and cases were observed after soldiers had slept at night in old ruins and caves. However, similar conditions prevailed in Malta during the same period. Had such a natural chain of infection been present here it seems probable that human cases would have occurred and have been recognised.

Toxoplasma Infections appear to be common to most forms of animal life and are very widespread. Amongst other things, they are a recognised cause of abortion in sheep. So far they have not been seen in animals in Malta; but this means very little. It is difficult to obtain suitable material for diagnosis from sheep and goats.

Parasitic Conditions

Oestrus Ovis Infestation. Sheep and goats in Malta are heavily parasitised by the sheep nostril fly, which, whilst in flight, squirts living larvae into their nos-

trils. In some countries humans are attacked occasionally and during the summer months it is customary for shepherds to wear a branch of leaves in their hats or to carry a leafy twig between their teeth to discourage the flies. In their natural hosts the larvae migrate to the frontal and submaxillary sinuses where they grow to a large size. In humans, the small, almost microscopic, larvae fail to grow and wander aimlessly around the back of the pharynx causing a most severe irritation for several days. Presumably a suitable larvicide would hasten recovery in such cases.

Larva Migrans. Attention has recently been given to the infection of children by the larvae of *Toxocara canis* (Woodruff *et al.* 1966). In their abnormal host these larvae can wander erratically producing granulomas, sometime affecting the eye and occasionally producing an encephalitis. An allergic skin test has been developed to demonstrate previous sensitisation, but clearly diagnosis can present difficulties and the nervous type of lesion may be commoner than is suspected. At this stage one can only say that puppies will naturally harbour much larger numbers of ascarids than will adult dogs, and therefore the practice of giving children a small puppy to play with can be dangerous unless that puppy is treated for worms at regular intervals.

Discussion

With the parasitic diseases we already have several examples where a parasite can produce serious effects when it gains entry into an unnatural host. Probably the most classic example of this is Hydatid Cyst in Man. Amongst viruses and protozoa also, a number have a wide distribution in nature, with man apparently playing the part of the unnatural or accidental host and it often seems that the animal has acquired a greater degree of tolerance than has man. It seems possible that we shall find a number of other supposedly human diseases to exist in nature in other forms of animal life. Curiously, the process does not often seem to work the other way round; man does not to any

degree act as carrier for the contagious diseases of animals. Perhaps this is because we are more interested in situations where "dog bites man" and have not looked hard enough for case where "man bites dog". Perhaps, in some cases, it is because animals have been here for much longer.

In an article of this length one can do little more than introduce the subject and pick from a wide field those points which are of more direct interest in Malta. This naturally leads to a somewhat uneven form of presentation.

In the experience of the author there has often been gain in discussing veterinary problems with those who have been trained in other disciplines and whose reading and approach come from a different angle. The foregoing is submitted with humility in the hope that the same process may work sometimes in reverse.

Acknowledgement

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References

- CACHIA, E.A. and FENECH, F.F. (1964) *Trans. Roy. Trop. Med. & Hyg.* 58, 234.
 CROWTHER, R.W. (1957) *Vet. Rec.* 69, 695.
 FOOD & AGRICULTURE ORGANISATION (1959) Joint WHO/FAO Expert Committee on Zoonoses, Second Report. Technical Report Series No. 169.
 FENECH, F.F. and GRIXTI, N. (1966) *St. Luke's Hosp. Gazette* 1, 64.
 GAMBLES, R.M. and COGHILL, N.F. (1948) *Annals Trop. Med. and Paras.* 42, 288.
 GRAY, M.L. and KILLINGER, A.H. (1966) *Bact. Rev.* 30, 309.
 HULL, T.G. *Diseases Transmitted from Animals to Man.* (Thomas C.C.)
 HARTLEY, E.G. (1964) *Vet. Rec.* 76, 555.
 KERR, W.R., COGHLAN, J.D., PAYNE, D.J.H. and ROBERTSON, L. (1966). *Vet. Record*, 79, 602.
 MARTIN, W.B., MARTIN, B., HAY, D., and LAUDER, I.M. (1966). *Vet. Rec.* 78, 494.
 NAGINGTON, J., TEE, G.H., and SMITH, J.S. (1965). *Nature*, 206, 505.
 OMAR, A.R., and KIRCH, D.A. *Vet. Rec.*, 78, 766.
 PETERS, D., MULLER, G., and BUTTNER, D. (1964). *Virology*, 23, 609.
 WOODRUFF, A.W., RISSERU, B., and BOWE, J.C. (1966). *Brit. Med. J.* 1, 576.

SANITARY ORGANIZATION IN MALTA IN 1743

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(Continued from Vol. I, page 59)

The configuration of the southern aspect of Valletta presented a different appearance in 1743 from the one we see to-day. Between *Porta del Monte* (now Victoria Gate) and Lascaris Tunnel stretched the Garden of the Grand Master originally planted by Grand Master Jean Paul Lascaris Castellar (1635-57). Over the tunnel stood the residence of the Superintendent of the Port. Beneath the Bastion of St. Barbara were built a number of grain stores, known as the Magazines of Perellos after their founder Grand Master Ramon Perellos (1697-1720), and a chapel (1712) dedicated to Our Saviour. This chapel, which has since been demolished, served for the celebration of the Mass for the crews kept in quarantine on their own ships in front of the wharf.

The quay was known as the wharf of the *Barriera degli infetti o della quarantena* because it was reserved for the unloading of goods and passengers from ships in quarantine. At its extreme end, beneath the Post of Castille, there was a hall for the detention of passengers and also the *barriera*, which was an arrangement of railings made of poles, bollards and beams intended to prevent passengers and crews from coming into close quarters with the inhabitants.

The magazines of Perellos and the chapel were demolished in 1853. The *Barriera* and the nearby arcades ("*loggiato*"), which together with the *barriera* served as a *Parlatorio* or speaking-place seem to have been removed at this period or somewhat earlier (11).

That part of the shore between Lascaris Tunnel and the present Custom House was, in 1651, turned into a small creek by Bali Fra Giulio Amati to provide a sheltered place for boats during bad

weather. It was known as *Porto Pidocchio*, or Port of the Louse, because, at the time of the Knights, the galley oarsmen used to go ashore in this creek to "bask in the sun and delouse themselves" (12).

During the 1743 plague precautions, boats were debarred from approaching that part of the wharf extending from Lascaris Tunnel to the *Barriera* but were made to discharge and embark men and goods only on that part of the shore that stretched inwards from *Porto Pidocchio* towards the Marsa.

On the 8th of June ships coming from Calabria and the Kingdom of Naples were allowed to enter harbour after being inspected by a Health Guardian who had to make sure that they carried no goods from Sicily. The Health Commissioner had to ascertain that the ships had not touched ports in Sicily and had had no dealings with Sicilian or other vessels coming from suspected places or with infected ships.

Ships from places south of Catania and Palermo were placed in quarantine for twenty-four days, but vessels coming from ports in Sicily north of these two towns or from Messina and its neighbourhood were driven away without being permitted to land cargo of any kind. This was the fate that awaited a vessel which reached Malta from Messina on the 7th June with Maltese passengers on board. Only dispatches and money were landed "with all due precautions" (13). On the 11th June two other ships arrived from Messina. They, too, were prohibited from "touching any part of the Islands of Malta and Gozo" and ordered to return to Messina but the Health Commissioners were permitted to receive moneys brought by these ships after the coins had been immersed in vinegar.

A part of the sea in what is now called

French Creek was reserved for the detention of ships under quarantine. This area was bounded to the south-west by the shore beneath the Heights of Kordin as far as Ghajn Dwieli then known as the Garden of Bailiff Francesco de Sousa Menezes; and to the south, east and north by a floating barrier made of a central pontoon and a series of masts chained to one another on each side of it. In this Quarantine Enclosure, sealed off from the rest of the creek, ships were anchored in the following order from south to north: those with a clean bill of health hailing from Portugal, Spain, France, Genoa, Leghorn and Civitavecchia; further on were moored suspected ships; and lastly vessels with a foul bill of health which were berthed immediately near the Military Guard House towards the Marsa in such a position that they were in constant view of the guards. Rowing boats were fastened close to the shore near the Guard House.

The Quarantine Enclosure was watched, day and night, by a number of armed guards under a knight who was allowed to leave his post to have lunch and dinner at his auberge but was expressly prohibited to "go hunting on Kordin Heights or to take mattresses to the Guard House". The sentries were distributed as follows: (a) on the pontoon moored in the middle of the creek and forming part of the floating barrier; (b) at the Guard House on the wharf; (c) on the mole near the garden of Bailiff Francesco de Sousa; and (d) midway between this garden and the Guard House. Apart from these soldiers, three boats of the Health Office also kept a constant watch inside and outside the Enclosure and carried at the prow the flag of the Order (white cross on a red field) as a distinguishing mark. Transgression of duty on the part of the soldiers and other employees was punishable by death.

The scope of the measures outlined above was to prevent persons, boats and ships from entering and leaving the Quarantine Enclosure and to prevent ships within it from communicating with one another. In fact the sentries had orders to shoot anyone disregarding their com-

mands. It is known that on the 11th October, 1744, an English sailor, who had defied the sentry's order not to go ashore, was shot dead by the guards (14). Only rowing boats were allowed to leave the Enclosure to proceed to the *Barriera* across the harbour. They did so at specified times, the signal being given by the hoisting of the flag of the Order on the stores of Grand Master Perellos already mentioned, where the Venerable Congregation of the Galleys had its offices. The boats carried a white flag as an identification mark and as a *laissez-passer*.

The *Barriera* was guarded by soldiers under the command of a corporal by day and of a knight by night (10th June). No one was permitted to approach the area without the licence of the Health Commissioners or of the Guardian of the Port or of the Health Office Clerk. At night two separate rounds of all ships in quarantine were made to ensure that no boats went in the vicinity of these vessels and that none of the crew communicated with the shore except in the case of an emergency. By a *bando* or proclamation of the 13th August, 1743, the inhabitants were warned not to go to the *bastione delle tre punte* overlooking the *Barriera* and not to talk to the passengers and crews detained in quarantine in that area (15).

Ships reaching harbour after night-fall were kept away from the quayside and made to anchor in the vicinity of the *barque de garde* near Fort Ricasoli until examined by the Health Commissioner the following morning.

A sanitary cordon was thrown round the Lazzaretto in Marsamxett Harbour to ensure that none of the persons confined therein absconded. Troops guarded the establishment by day and by night. Sentinels were posted at strategic points of Manoel Island to keep unauthorised persons at bay and given instructions to shoot anyone disobeying their orders. The Health Commissioner himself had to announce his presence when entering the Lazzaretto by sea by hoisting a flag on his boat.

On the 11th June a more vigorous surveillance was imposed along the shores

of Malta. Day duty was performed by the *soldats des vaisseaux* and by the *canoiers de la ville* while the night watch was entrusted to the *tourriers* and the *guardiens* provided by the Municipality.

This sanitary cordon stretched from north to south along the eastern seaboard and comprised the following towers: Ta' l-Aħrax Tower (Torri l-abjad), Torri l-aħmar, St. Paul's Tower, Qawra Tower, Ghallis Tower, Torri Qaliet Marku, Madalena Tower, St. George's Tower, Notre Dame de la Grace Tower (Torri tax-Xgħajra — now demolished), Żonqor Tower, St. Thomas Tower, Xrop il-għagin Tower, Delimara Tower, Ras iċ-ċaġhaq Tower, San Luciano Tower, Post tax-xaqqa, Torri Wardija (near Bubaqra), Post ras bajjada, Torri tal-Hamrija and Post Hagra s-sewda.

Ships attempting to land men or cargo were warned to keep off and go out to sea again; in case of non-compliance they were to be fired at by musketry or artillery. This rule was relaxed only in case of stormy weather when there was the risk of shipwreck. In such a circumstance the ship was allowed to drop anchor but not to disembark crew or goods or to hand in bills of health or letters.

One of the theories that tried to account for the origin and diffusion of plague ascribed the disease to a "vitiated" or "infected" atmosphere. Putrefaction was especially feared. In order to minimise the danger from this alleged source the Grand Master issued a *bando* which laid down the conditions under which horses, mules, dogs and cats dying in Valletta, Floriana, Senglea, Birgu and Bormla were to be buried. These animals were to be interred in specified places outside the fortifications under two "palms" of earth so that they would be well covered from view and their stench prevented from reaching the neighbourhood (16).

Although the epidemic at Messina had abated towards the end of the year, the Health Commissioners of Malta did not relax their quarantine measures. They continued to be as strict as ever with all shipping even with units of their own navy in spite of the fact that these ships had not touched any Sicilian Ports; thus,

for instance, a *tartana* though coming from as far north as Civitavecchia and Naples was placed in quarantine on the 24th December with its crew of 168 men and 25 passengers. Among the latter was the new Inquisitor to Malta, Mgr. Paolo Passionei, who was made to spend his quarantine at the *Giardino detto de Bichi* (17).

There was still one contingency that exposed the inhabitants of Malta to the risk of infection in the eventuality of a person absconding from quarantine and taking refuge in a church. In those days chapels and churches enjoyed the privilege of sanctuary. This meant that if a transgressor of the law entered a church or other building with ecclesiastical immunity the police had no right to enter the premises and capture him. There was, therefore, the possibility that escapees from quarantine or the Lazzaretto would avail themselves of this protection to foil the public health authorities with possible fatal consequences to the community if the escapees happened to be affected with plague. Suspension of this privilege of sanctuary pertained only to His Holiness the Pope. Temporary abolition of sanctuary had been sought and obtained by the Order on previous occasions from 1705 onwards. Recourse was, therefore, made in 1743 to His Holiness to discontinue this privilege for a period of ten years to enable the Order to remove from churches and other immune places all those suspected of harbouring contagious illness and to hand them over, with their personal belongings, to the sanitary authorities. The assent of the Pope reached the Grand Master, through the Bishop of Malta, on the 7th December, 1743, and in this way a vulnerable breach in the internal defences of the public health organisation was effectively healed (18).

The last hurdle which the Order had to overcome was of an economic kind. The disruption of commerce with Messina and other places in Sicily brought many Maltese ships to a standstill with consequent hardships to their owners and crews. It also "reduced to extreme misery the poor of the Island and especially of Gozo

who were engaged in the cotton trade, the weaving of cloth and other manufactures". The government felt it its duty of "Christian charity and especially of the pious institution of this Sacred Order" to help these people. An "ad hoc" commission was appointed on the 16th November, 1743, to provide work for the unemployed and to furnish adequate financial relief to the infirm (19).

No further casualties were reported in Messina after the 8th September, 1743, but not before 43,400 citizens had been carried off; sporadic cases, however, continued to crop up in its environs over a protracted period. On the 11th December, 1743, a certain Dr. Pietro Polacco, a Venetian physician, was called to Messina to direct a "general depuration" of the city. The interiors of the houses were cleaned with salt water and then white-washed; the rooms where plague patients had died were fumigated with a mixture containing naval tar, sulphur, incense and other ingredients; cotton goods were immersed in boiling water and even weapons and jewellery were disinfected with vinegar. These operations are described in great detail in a lengthy communication, signed by Dr. Pietro Polacco himself, which was sent to the Grand Master on the 28th February, 1744, by the Senate of Messina. Yet in spite of this extensive cleaning up of the city, Messina had not yet been allowed to resume free trade communication with the rest of Europe by April, 1745 (20). The Order of St. John took no risks with regard to Malta and it was only on the 23rd February, 1746, that the Grand Master considered that the threat of plague had vanished, that it was safe to call off the extraordinary quarantine restrictions and dissolve the special Commission of Knights appointed on the 29th May, 1743 (21). He did so not only with feelings of relief but also with pride at the success of the security measures imposed by the Commission so much so that it was decided to mark the deliverance of Malta from plague by the striking of a commemorative bronze medal.

The scene portrays the St. Elmo extremity of Valletta protected by a barri-

cade of stakes. To the left rises an obelisk bearing a civic crown near the top, in honour of the Grand Master, and a Greek legend on its base. This inscription is a motto taken from a medal of the Emperor Trajan and meaning Protector of the City. On the cornice of the base stands a cock, a symbol of vigilance. Round the margin of the medal are the words TUTATORI SUO, derived from a medal of Emperor Probo and signifying "To its protector". The bottom carries the date 1743 (22).

When we survey the arrangements made by the Order of St. John of Jerusalem we are struck by the lack of purely medical provisions and by the absence of physicians among the Commissioners and the other participants in what today would be considered to be a pre-eminently medical enterprise. In delivering judgment, however, we must bear in mind that in 1743 the discipline of public health as a special branch of medicine had not yet arisen and that medical science knew nothing about the aetiology and propagation of plague. Indeed, medical progress in the 18th century was slow and painful not only as regards aetiology and pathology of disease but also as regards therapy. In fact how would Maltese physicians have treated their plague-patients if the epidemic had reached the Island? They would certainly have followed the current methods of treatment in vogue at the time in Europe as set forth in one of the latest manuals on the management of plague. A copy of this *Trattato de' remedj contro la peste* ("Treatise on remedies against Plague") is attached to the other papers forming the collection of documents on which this study is based (23). It was written by a Signor Elvezio, physician to His Royal Highness the Duke of Orleans and published in Venice in 1743 — the same year of the Messina pestilence.

Treatment consisted in the administration of emetics, such as preparations of ipecacuanha and of antimony, purges and bloodletting. Great store was laid on the promotion of sweating by a so-called "anti-pestilential sudorific" containing a

dried extract of the gall of the pig and powdered liver of vipers. A decoction of quinine was also recommended for the same purpose. The idea behind these measures was to rid the body of the poison of plague by every evacuant means. It was, however, realised that this drastic treatment weakened the patient to a great extent. To counteract this unwanted effect, the patient was given a Gold Tincture consisting of gold dissolved in a solution of nitric acid, oil of camphor and alcohol.

Opium was prescribed with great caution to combat restlessness and delirium. The buboes were treated by the application of emplastra to promote pus formation and then incised and evacuated. To escape catching the disease, several preservatives were available. These included the carrying on one's person of a lemon into which dried cloves were inserted, or else a small bag containing nutmeg, camphor and other aromatic substances.

Persons were fumigated or smoked with burnt gunpowder and asafetida. The air in houses was purified in a like manner or else by the heating of vinegar, cloves and other herbs.

It is obvious, from the foregoing considerations, that physicians were too overwhelmed by the medical ignorance of the time to make a valid contribution in the fight against plague. They were only aware that there were endemic foci of plague which periodically flared up to assume epidemic proportions and that these foci were in the Levant from where they invaded Europe along the trade routes by land and by sea. The impact of bacteriology on the investigation of the causes of disease started to make itself felt only one hundred years later while the causative agent of plague and its mode of conveyance to man by the flea from infected rats were not discovered until 1894 and 1897 respectively.

On the other hand, when we compare the sanitary measures enforced in 1743 with modern methods of plague control

we find that there were only a few of the present procedures which were not applied in Malta in those days, i.e. the search for signs of plague in the rodent population of the Island and the launching of a drive for the destruction of rats. Except for this neglect of the rat, the sanitary precautions planned and executed by the Knights are still essentially those adopted by the public health authorities of our own day, i.e. (a) quarantining of infected areas and of ships hailing from them, (b) segregation of contacts, and (c) isolation and disinfection of suspected merchandise. Although, therefore, the Knights were far removed from us in scientific knowledge we cannot fail to be impressed by the soundness of their principles of public health prophylaxis, the rationality of the methods employed and the welding into an integrated sanitary system of their naval, military and economic resources. We are also reminded that in the fight against disease the wise utilisation of non-medical procedures and personnel has its place as much as the application of the results of medical knowledge and research.

References

11. *L'Ordine*, 21st October, 1853, p. 4179.
12. REBOUL, G.: *Giornale de' successi dell'isola di Malta e Gozo*, Malta, 1935, pp. 76 and 100.
13. Archives 269, fol. 251t. Royal Malta Library.
14. REBOUL, G., *op. cit.*, p. 65.
15. Archives 428 (1736-1744), fol. 167, Royal Malta Library.
16. *Ibid.*, fol. 167.
17. Archives 269, fo's. 253, 265t and 268, Royal Malta Library.
18. *Ibid.*, fol. 263t.
19. *Ibid.*, fol. 263.
20. TURRIANO, O., *op. cit.*, pp. 1-99.
21. PACIAUDI, P.M.: *Medaglie rappresentanti i più gloriosi avvenimenti del Magistero di S.A.E. Fra D. Emmanuele Pinto*, no date, no place of publication, no pagination.
23. Archives 6464, Royal Malta Library.

(References 6 and 7, in the first part of this article should have read "Royal Malta Library", instead of "Royal University of Malta".)

FAREWELL TO A MASTER



On the 20th April Professor Walter Ganado had his sixtieth birthday and time irrevocably brought to a close his service at St. Luke's Hospital; he had worked in the Health Department since 1932 and many, probably like him, could hardly realise this severance would come. He struck us that morning as if the occasion had left him rather sad, but when the nurses and sisters who had long worked with him, in the most informal manner possible, presented him with a parting gift, he soon recovered his habitual gaiety of spirit. He told his well-wishers that they must never think that the professor is the most important person in the wards. For a moment we thought he was going to admit what everybody thinks to be the case — that the most important person is the ward sister. But no! Walter, as usual, was a little wiser than us. "The most important person", he said, "is the patient". A few days later, professor Ganado was the guest of all his colleagues at a luscious cocktail party, on the terrace of the Medical School.

We would hate to write of him in utter panegyric. One only speaks like that of one's colleagues when they are safely dead and cannot use one's words for any practical purpose. His reputation for taciturnity is not great; but that is, perhaps, after all one of his virtues. Richard Garnett put it well:

'I hardly ever ope my lips', one cries;
 'Simonides what think you of my rule?''
 'If you're a fool, I think you're very wise;
 If you are wise, I think you are a fool.'

Walter Ganado has always been generous with his thoughts and sentiments. A born teacher, he has a special gift for the simplification which lights up a complicated medical problem. He taught medicine to many of his present colleagues in a way they can never forget. Best of all he succeeds in imparting to his listeners many (though, of course, not all) of his enthusiasms. Unexpectedly the present writer owes to him his appreciation of

the drama — all through a glowing description of "Cavalcade", as Walter had seen it on the London stage, given during one of those night duties at the old Central Hospital.

We are happy to know a charming daughter, in the Department of English, keeps the Ganado link with the University. We wish ourselves that, for many more years professor Walter Ganado and Mrs. Ganado (who could not share his characteristics better had she been a sister instead) should go on lighting the medical and social life of Malta with their irrepressible wit and brilliance.

The three admirable papers in this issue from the department of physiology are presented as a special tribute from the first department over which he presided, a tribute with which all the medical profession in Malta associates itself.

PUBLICATIONS LIST

Here are further additions to our list of scientific publications since 1961 by graduates of our medical and dental schools.

BANNISTER, W.H. 1963. Acid secretion and oxygen consumption by isolated frog gastric mucosa. *Biochem. J.* 89, 62P.

BANNISTER, W.H. 1964. Effect of thiocyanate on secretion of acid and uptake of oxygen by gastric mucosa of the frog. *Nature*, 203, 978.

BANNISTER, W.H. 1965. The relation between acid secretion and oxygen uptake by gastric mucosa of the frog. *J. Physiol.* 177, 429.

BANNISTER, W.H. 1965. The effect of some substrates and metabolic inhibitors acting on the respiratory chain on acid secretion and oxygen uptake by gastric mucosa of the frog. *J. Physiol.* 177, 440.

BANNISTER, W.H. 1966. Acid secretion by frog gastric mucosae incubated in chloride-free medium. *Amer. J. Physiol.* 210, 211.

BANNISTER, W.H. 1966. The effect of oligomycin and some nitrophenols on acid secretion and oxygen uptake by gastric mucosa of the frog. *J. Physiol.* 186, 89.

GILLES, H.M. and MCGREGOR IO. 1961. Studies on the significance of high serum gamma-globulin concentrations in Gambian Africans. III. Gamma-globulin concentrations of Gambian women protected from malaria for two years. *Ann. trop. Med. Parasit.*, 55, 463.

GILLES, H.M. 1961. The natural history of "Stable" *Falciparum* malaria in the pre-school child. 10, 293.

GILLES, H.M., CAPPS, F.P., JOLLY, H. *et al.* 1961. The existence of the glucose-6-phosphate dehydrogenase deficiency trait in Nigeria and its clinical implications. *Ann. trop. Med. Parasit.* 55, 64.

GILLES, H.M. and HARRIS, R. 1961. Glucose-6-phosphate dehydrogenase deficiency in the peoples of the Niger delta. *Ann. hum. Genet., Lond.* 25, 199.

GILLES, H.M., WATSON-WILLIAMS, E.J. and WORLEDGE, S.M. 1961. A note on the treatment of *Necator americanus* infections with bephenium hydroxynaphthoate. *Ann. trop. Med. Parasit.* 55, 70.

GILLES, H.M., EDOZIEN, J.C. and UDEOZO IO. 1962. Adult and cord blood gamma-globulin and immunity to malaria in Nigeria. *Lancet*, ii, 951.

GILLES, H.M. Filaricides — Symposium on chemotherapy. *Pract.*, 188, 77.

GILLES, H.M. and TOMPKINS, A.B. 1962. Treatment of intestinal parasites in children. *Clin. Pediat. (Phila.)* 1, 32.

GILLES, H.M. and WALSHE, J.M. 1962. Haematological and biochemical observations of a herd of Gambian cattle. *J. comp. Path.* 72, 439.

GILLES, H.M. and HENDRICKSE, R.G. 1963. The nephrotic syndrome and other renal diseases in children in Western Nigeria. *East Afr. med. J.* 40, 186.

GILLES, H.M. and HENDRICKSE, R.G. 1963. Nephrosis in Nigerian children. The role of *P. malariae* and the effect of anti-malarial treatment. *Brit. med. J.*, ii, 27.

GILLES, H.M., CAPPS, F.P., JOLLY, H. and WORLEDGE, S.M. 1963. Glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Nigeria: their relation to the use of prophylactic vitamin K. *Lancet*, ii, 379.

GILLES, H.M. Akufo — an environmental study of a Nigerian village community. Ibadan University Press, pp. 80, January, 1964.

GILLES, H.M. 1963. Epidemiological and clinical aspects of hookworm anaemia. Ann. Soc. Belge. Med. Trop., 4, 627.

GILLES, H.M. 1963. Undergraduate medical education in the tropics. Abstracts of the papers, seventh international congress on tropical medicine and malaria, Rio de Janeiro, Brazil, p. 379.

GILLES, H.M., WILLIAMS, E.J. and BALL, P.A. 1964. Hookworm infections and anaemia. Quart. J. Med., 33, 1.

GILLES, H.M. and BALL, P.A. 1964. Guinea-worm infection and gastric function. Ann. trop. Med. Parasit., 58, 78.

GILLES, H.M. 1965. Teaching of preventive medicine in the tropics. Lancet, ii, 280.

GILLES, H.M., PI-SUNYER, F.X. and WILSON, A.M. 1965. *Schistosoma haematobium* infection in Nigeria. I. Bacteriological and immunological findings in the presence of schistosomal infection. Ann. trop. Med. Parasit., 59, 304.

GILLES, H.M., LUCAS, A., ADENYI-JONES, L. *et al.* 1965. *Schistosoma haematobium* infection in Nigeria. II. Infection at a primary school in Ibadan. Ann. trop. Med. Parasit., 59, 441.

GILLES, H.M., LUCAS, A., LINDNER, R. *et al.* 1965. Infection in boatyard workers at Epe. Ann. trop. Med. Parasit., 59, 451.

GILLES, H.M. 1965. L'enseignement de la santé publique a l'Université d'Ibadan - Nigeria. Ann. Soc. Belge Med. Trop. 45, 603.

GILLES, H.M., ADETOKUMBO, O.L., ADENIYI-JONES, C.C. and COCKSHOT, W.P. 1966. Radiological changes after medical treatment of vesical schistosomiasis. Lancet, i, 631.

GILLES, H.M. 1966. Poliomyelitis vaccination in Ibadan, Nigeria during 1964 with oral vaccine (Sabin strains). Bull. Wld. Hlth. Org. 34, 865.

GILLES, H.M. 1966. Malaria in children. Brit. med. J., ii, 1375.

GILLES, H.M. and GELFAND, M. 1966. Filling defects of the bladder on intravenous pyelography in children passing schistosome ova in the urine. J. Trop. Med. Hyg., 69, 4.

VELLA, F. 1966. Haemoglobin C trait in Saskatchewan. Can. Med. Ass. J., 95, 1135.

VELLA, F. and CUNNINGHAM, T., 1967. The electrophoretic pattern of haemoglobin in newborn babies, and abnormalities of haemoglobin F synthesis in adults. Can. Med. Ass. J., 96, 398.

VELLA, F., ISAACS, W.A., and LEHMANN, H. 1967. Haemoglobin G. Saskatoon. Can. J. Biochem., 45, 351.

MEDICAL NEWS

We congratulate professor Joseph V. Zammit-Maempel, M.D., F.R.C.P., who has been professor of *Materia Medica* and *Therapeutics* and on the staff at St. Luke's since 1947 on being appointed Senior Physician at the Medical and Health Department and Professor of Medicine at our University.

We also congratulate Sister Bernardette Fava, S.R.N., N.Adm.C. (Hosp.), on her appointment as assistant matron at St. Luke's.

Dr. D. L. Gullick, an under-secretary of the British Medical Association, whilst on a tour of the overseas branches, visited Malta from the 8th to the 11th December last. The council of the local branch held a meeting at which doctor Gullick was present and a reception was afterwards held in his honour. An invitation was made, through Dr. Gullick, to the parent body to hold its annual clinical meeting in Malta. We are very glad to state that this invitation has been accepted and the Malta medical profession can look forward to the pleasure and honour of playing host to what we hope will be a considerable number of their colleagues from Britain sometime in April 1969.

Professor Victor Griffiths was last January elected to the presidency of the Malta Branch of the British Medical Association.

Dr. Joseph Sammut was the winner of the B.M.A. (Malta) prize competition with an essay on "Middle Ear Acoustics", illustrated with microphotographs taken by him.

By kind permission of the University, the Malta Branch of the B.M.A. is now holding its meetings in the Conference Hall of the Medical School. These fine premises are an inspiration to audience and speakers. On the 19th December, the branch welcomed Dr. M. Lederman of the Royal Marsden Hospital, who spoke on "Radiotherapy and Cancer".

A film on "Mitral Stenosis", shown on the 29th December, was introduced by Dr. Victor Captur and Dr. J. Rizzo Naudi.

Professor C. Bruce Perry, of the University of Bristol, lectured on the 24th February on "The Diagnosis of Acute Rheumatism" and on the 27th, on "Some complications of Diabetes".

Dr. R. L. Cheverton, a former Deputy Director of Medical Services of Nigeria and Director of Medical Services in Ghana, spoke on the 2nd February on "Medical Problems in West Africa".

On the 7th March, doctors V. Captur, J. L. Grech and J. L. Pace collaborated in presenting a study of "Endocardial Fibroelastosis". On the 16th March, Dr. E. M. Mary's Hospital, London, gave an extreme-Bestreman, consultant cardiologist at St. mely practical and informative address on "Treatment of Cardiac Arrhythmias".

On the 14th April, Dr. W. Crofton, professor of Respiratory Diseases and Tuberculosis at the University of Edinburgh, lectured on "The Chemotherapy of Non-tuberculous Pulmonary Diseases".

On the 3rd April, Dr. Leslie Pace read a short paper on "The interconnection of the muscle layers of the human colon". This was a report on original work on which he is now engaged. This was followed by a lecture on "The disease: Tobacco smoking", given by Dr. Lennox Johnston. Dr. Johnston, a pioneer in this special field and a forerunner of the great discoveries which inculpated tobacco smoking as a cause of respiratory tract cancer, is now retired and living amongst

us. His talk was very interesting, but the discussion which might have followed it did not amount to much, probably because his listeners were quite convinced of the truth of his thesis, which was not surprising at a medical gathering. This was a case where things end "not with a bang, but a whimper".

The Branch was especially glad to welcome Sir Victor Negus, the eminent otorhinolaryngologist, chairman of the trustees of the Hunterian Museum. Sir Victor broke a holiday to address the branch on "The Value of Comparative Biology". He presented the Dean of the Medical Faculty with two valuable books, the "Descriptive Catalogue of the Pathological Series in the Hunterian Museum", and his own work "History of the Trustees of the Hunterian Collection".

Mr. H. S. Shucksmith, of the Leeds General Infirmary, lectured on the 15th May on "Blocked and Bursting Blood Vessels". Altogether the B.M.A. Malta Branch is having a very active life, and, as one of our visitors was heard to remark, it has a lecture programme which many other branches might envy.

Professor Martin A. Rushton, Chairman of the Educational Committee of the General Dental Council, visited the Dental School, as an official of the General Dental Council.

Professor T. N. A. Jeffcoate, professor of Obstetrics and Gynaecology of the University of Liverpool, Professor H. G. Miller, professor of Neurology of the University of Newcastle-upon-Tyne, and Professor H. W. Rodgers, professor of Surgery at Queen's University of Belfast, formed a delegation of the General Medical Council of Great Britain which visited our University and the Medical School, at the invitation of the Vice-Chancellor.

Sir Clifford Naunton Morgan, of Bart's, Professor A. S. W. Whitfield of Birmingham, Professor Ian Donald from Glasgow and Sir Derrick Dunlop from Edinburgh, are prospective external examiners in the coming session at the medical school.

We are glad to express the appreciation of the Medical Faculty in Malta to the Wellcome Trust for its generous gift

of the sum of £3500 to the physiology department for the purchase of a preparative ultra-centrifuge.

At a pleasant little ceremony in Dr. T. Agius-Ferrante's Office, in Children's Ward A, the honourable Dr. A. Cachia-Zammit accepted, on behalf of the department, gifts to the hospital. Riker's, through Mr. Vella, gave 2 pediatric text-books, Mr. Louis Vella a complete resuscitation kit, Messrs Nestles an artificial respirator, Barclays Bank a portable incubator, Mr. Joseph Gasan three folding bassinets and Messrs Farsons Cisk Ltd. a heart auscultation device. The gentlemen and firms concerned certainly deserve thanks and praise for being so public spirited.

The "Associazione Otologica Ospedaliera Italiana", meeting out of its own country, held a successful congress in Malta between the 2nd and the 5th of May.

PERSONALIA

This magazine does manage to get to almost every medical and dental graduate of our university, and we feel it is a good thing to print a few notes about ourselves as individuals, apart from the purely professional and rigidly scientific aspect. So, here goes.

Herbert Gilles ('46), of whose publications we publish an awe-inspiring list, is now Senior Lecturer in tropical medicine at the celebrated school of the University of Liverpool, and honorary consultant physician to the Liverpool Regional Hospital Board. These data draw attention to the fact that there are such things as *senior lecturers* in some universities and to the other fact of the connecteion between Malta and Liverpool University, an association which was probably started by the late Dr. Attilio Critien, a former C.G.M.O., who not only took a diploma from the Mersey city but also married a lady from the nearby charming village of Great Crosby. Gilles, who had been professor of Preventive and Social Medicine at Ibadan, in Nigeria for 2 years, now also holds an honorary visiting professorship at Lagos. When in New Delhi, representing the

University of Liverpool at a world conference on medical education in 1966 he met Albert Zahra, now with W.H.O. The twain had not met for 17 years.

Joseph Galea ('49), for many years a pathologist in Quebec, has now moved to Lakeshore General Hospital in Montreal; he is also a demonstrator at the celebrated McGill University. He lives in Revere Avenue in the town of Mount Royal, which is a sort of millionaire's quarters in the centre of Montreal. He got to the city just in time for Expo '67.

There is a large colony of Maltese doctors in Australia. Albert Vella ('55) was here on a well earned holiday last January. He works in Melbourne, as do Gaetano Briffa ('55), and Edward Gatt, who is married to Maurice Gatt's sister. Other Maltese doctors are Thomas Pirotta, who graduated in Australia, is a Fellow both of the British and of the Australian Colleges of Surgery, and works in Melbourne, and Roland Buhagiar, who graduated in Sydney. Carmelo Cassar ('49), practises in Sydney.

Congratulations to Mr. Joseph Attard ('55) who has just been elected a Fellow of the Royal College of Surgeons of England. He has moved from Worcester to Luton in Bedfordshire where he is now Senior Registrar in Surgery at the Luton and Dunstable Hospital.

To make extra sure that there should always be a doctor in the family, Roy Schembri Wismayer ('64), on the 1st April last married Dr. Mercedes Zarb-Adami ('64). Godfrey Zarb-Adami married Miss Tanya Bonello on May 21st. The Schembri Wismayers constitute a remarkable family, since there are six (without counting the latest acquisition) who have taken the Hippocratic oath. Salvino ('55) is a resident M.O. at the Mental Hospital at Attard; Lino ('55) is at Victoria Hospital in Gozo; Joseph ('58) is Senior Orthopaedic Registrar at the Royal Surrey County Hospital in Guildford; Walter ('58) is Senior Registrar in Anaesthesia at Heatherwood Hospital, Ascot, in Berkshire; Albert (62) is Senior House Officer at St. Leonard's Hospital, in London; Roy is for the moment in Malta. We wonder quite se-

riously whether six doctors in one family constitute a world record.

Alexander Galea ('64) recently married Miss Gail Hellmut, at the well known Jesuit church in Farm Street, London. Father J. Brooks, S.J. officiated.

Dr. Francis Vella ('61) married Miss Vivienne Grech on the 25th May. Dr.

Franz V. Consiglio ('58) married Miss Joan Schranz on the 28th May.

Finally, our hearty congratulations to Joseph Ebejer-Redman who passed the finals for F.F.A.R.C.S. last February. He is now an anaesthetist at Milford Chest Hospital and attached to Charing Cross Hospital, London.



NOTICE

This gazette is published biannually in June and in December. Contributions for the next issue are to reach the editor at the Bacteriology Laboratory, St. Luke's Hospital, Malta, by the 1st November. Reprints of individual articles will be available to contributors by arrangement.

Readers are specially requested to co-operate in making this periodical as informative as possible by sending in information about their own professional and social activities and about those of their friends.

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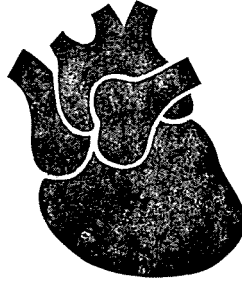
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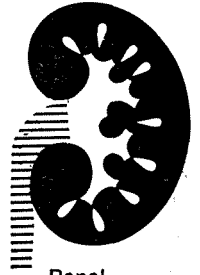
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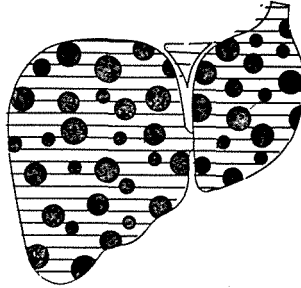


Cardiac

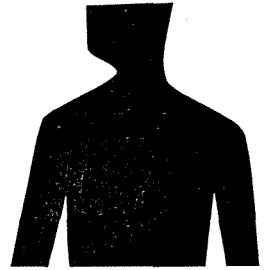


Renal

Hepatic



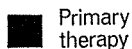
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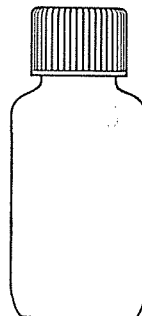
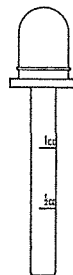


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*H. Winner and R. Hurley, *Candida Albicans*, 1964, page 184
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