THE

ST. LUKE'S HOSPITAL GAZETTE

MALTA DECEMBER 1970 Vol. V No. 2

Published for the Consultant Staff Committee, St. Luke's Hospital, Malta, and the Medical and Dental Surgery Faculties of the Royal University of Malta.

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AFTER FIVE YEARS

By this number, the tenth issue, this periodical completes the fifth year of its existence. One is happy to note that the fear of at least one pessimist that there would not be enough papers to publish has proved groundless and it does seem as if in this case the demand has created a supply. The standard also fortunately appears to satisfy competent judges.

What one could perhaps call a side-effect of publication is that, through care to send copies to those of our graduates who are abroad, the periodical has served as a link for a widely scattered fraternity. In this issue, apart from having the honour of publishing a contribution from one who could be called, with little fear of contradiction, the best known surgeon in South Africa, we are glad to publish contributions from colleagues in London, Leeds, Oxford, Toronto and Australia. Many read our news columns with interest and we hope they will continue to do so. A journal is to a large extent what its contributors make it and we wish very sincerely that this state of happy symbiosis should continue to prevail.

TWO DISEASES

At this juncture two diseases occupy our minds: exotic cholera and (should one say?) homely Brucellosis. Cholera is one of the great epidemic infections whose movements across the earth are followed with dread. In spite of optimistic considerations, we believe its occurrence could still constitute a major disaster and one dreads what is bound to happen in countries with bad medical services and a poor organization in general. In civilised countries our advantage over our ancestors is that we know precisely what causes the disease and this gives us a means of effective control. The knowledge is now possessed by all but there are countries where this cannot be applied. Never, however, as in the occurrence of a serious epidemic disease is the brotherhood of man so much made manifest and one can only hope that the various countries will have the good sense to make use of goodwill as it is manifest through the World Health Organization. One recalls the Egypt outbreak of 1947-48 and the way in which it was controlled. The problem is much more difficult now, which only makes its control more important.

So far, thank Heavens, our country has been spared but this is another case when the price of safety is eternal vigilance. We are very close to Libya and, by air, to many other countries in which the disease has occurred. In cholera, vaccines are far from being the most important means of prevention. What has been achieved in illnesses like poliomyelitis has not been achieved in cholera. In fact, whilst one notices the enthusiasm with which the public has sought vaccination, one feels it is only proper to let people know that this is only one means of defence and that it is not the most effective. It is strange that, in this day and age, we should have to revert to isolation and quarantine measures, but strange though it is, it is also very necessary. Doubtless many will be irked by restrictions on their movements but the health of the majority must remain the primary consideration. One cannot, meanwhile, help thinking that we have here a dramatic reminder that whilst certain diseases can go underground for a time they are still with us. He who thinks that bacteria and viruses have been abolished from our world is a poor biologist and would be a most inefficient public health man.

Brucellosis, widespread as it is, is still to a considerable extent our own special problem. Between 1956 and 1968 largely through the activity of our own veterinarians and of the work of the Brucellosis research laboratory at Ghammieri under Mr. G. G. Alton, the illness was brought under control as it had never been brought before and the incidence amongst human being, reflecting what was happening in the animal world, fell from 522 in 1955 to the record low figure of 14 in 1968. In 1968 Mr. Alton was transferred by the FAO to Buenos Aires and his expert services were no longer available. By that time, we had a vaccine, Elberg's Rev. I vaccine, whose effectiveness had been proved elsewhere and also under local conditions. There was legislation making the vaccination of new born kids compulsory, but there was no co-operation on the part of goat breeders and no effective means of getting it. In 1969 there were 57 cases of Brucellosis reported and this year, up to the end of October, there have been at least, 45 cases. Surely here we had — or may still have — a chance of ridding our island of what has been a long-standing stigma. Mr. Alton has returned for some few months to Malta to give another look and a helping hand. It is possible that the fight against Brucellosis will have been vigorously restarted. It is up to the Ministry of Health and the Government in general to see that there will be no retrogression and, now that we are so far ahead, that we should go on at least to elimination of the disease amongst human beings. Then indeed will the name "Malta fever" for so long and so properly resented, be a misnomer to be discarded for ever.

HAS HEART TRANSPLANTATION ANY FUTURE?

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This is the second Sir Denis Browne Memorial lecture, delivered on the 12th September, 1969, under the auspices of the Malta Section of the International College of Surgeons, at the Medical School of the Royal University of Malta.

We have come here tonight to commemorate a man who set down so many stepping stones that he could have built a stairway to heaven. I consider it a great honour to have been invited by the Malta Section of the International College of Surgeons to give this lecture and to recall this great man to your mind. I hope that I will be able to do justice to his memory.

On the 3rd December, 1967, a young girl and a mother crossed a street three miles away from one of the major hospitals in Cape Town. They were both hit down by a motor car; the mother was killed instantly, and the girl received irreversible brain damage. She was admitted to hospital within minutes, and after examination by the neurosurgeons and neurologists, they declared that her brain was dead, and there was nothing in the power of medicine that could save her life.

In a room of the hospital, not very far from where the girl lay dead, there was a man suffering from an irreversible heart condition, in the terminal stages of this disease, not responding any more to all the treatment that the medical profession could think of.

After the girl had been declared dead, permission was obtained from her father. He was asked to donate the heart of his daughter to a man that he had never seen and whom he did not know, to a man his daughter would never see. He was asked to donate this heart in an attempt to alleviate the sufferings of this man, and in an attempt to prolong his life. The father said that if there was nothing more that could be done for his daughter, then he believed that it would have been her wish that her normal heart be removed in an attempt to save this man's life.

A human to human heart transplant was performed that night on this man, and within hours the news crossed all the oceans that surround Cape Town. Overnight the heart transplant became world news. It was received with great enthusiasm in some quarters, while other quarters expressed bitter criticism. And every few months the question was asked: Is there any future for heart transplantation?

Now we must ask ourselves: Why should'nt there be a future for heart transplantation? Is it perhaps because we are crossing the ethical and moral boundaries of medicine? And perhaps we should deal with this question first to see whether there is any future in human transplantation, because, if we behave unethically and immorally, then there is no future for this operation. I would, therefore, like to examine the three major points of contention. First, is the act itself moral and ethical? Second, does the recipient receive ethical and moral treatment? And lastly, do the donors receive ethical and moral treatment?

Let us deal with the first question. Is the heart transplant, the act itself, ethical? News coverage of transplantation in the popular mass media has been widespread and on the whole enthusiastic, and, unfortunately, too often sensational and misleading. It has been misconceived in certain sections of the public both as a panacea and as an unethical and unjustified form of treatment. We believe that neither of these contentions is accurate. Within our limited experience of immu-

nology and immunological reactions on transplanted organs, we believe that it is not possible to prevent the rejection of a transplanted organ completely. In other words, we do not believe that a heart transplant is a curative procedure. We do not believe that the heart disease from which the patient suffered will be cured. But we do believe that we are able to palliate; to alleviate his symptoms and possibly to prolong his life. This is not unheard of in medicine. Palliative procedures are performed every day. Most of the operations on cancer of major organs, such as removal of the lung for bronchial carcinoma, the removal of the oesophagus for oesophageal carcinoma, and even the removal of the stomach for gastric carcinoma, are not curative procedures. We cannot tell the patient that by removing his cancer we will cure him. But we can tell him that with this operation we can alleviate his suffering and may even be able to prolong his life. So palliative procedures are certainly not unheard of in medicine.

It has often been said that the money that is spent on this operation and the number of persons involved are unjustified by the limited scope of heart transplantation. It has been said that we spend so much money and use so many people and yet can only treat a few patients in one year. This same criticism was levelled at open heart surgery using the heart-lung machinery when this new type of operation first began to be performed. It was said that the operation was too big, that it was too expensive and too many people were employed. But gradually we solved these problems and we simplified the procedures and today open heart surgery, using the heart-lung machine, saves hundreds of thousands of lives.

I believe that to curb heart transplantation at this stage will be very short-sighted. I believe that organ transplantation is the surgery of the future and the treatment of many diseases for which we can do nothing today. Therefore, I believe that there is nothing new in the act of transplantation; it is a palliative procedure, and as such we can accept it in medicine.

The next question to consider is whether the recipient receives ethical treatment. As has been pointed out, heart transplantation is not a curative but a palliative procedure, and patients should only be submitted for heart transplantation when other forms of surgical treatment have failed. In other words, we must select the patients on three criteria. The first criterion is that operation is indicated only on patients with incurable heart condtions; secondly, we must only operate on them when all other forms of treatment have failed; and thirdly, we must only operate when the disease has reached the terminal stages. If we accept and apply these three criteria, then I believe that the doctor performs his duty by doing a heart transplant. It is only right to give the patient all the treatment that is available and, if a particular centre is equipped and can do a heart transplant, then the doctors will not be doing their duty unless they give the patient this chance to save or, at least, to prolong his life.

The last question is whether the acquisition of donor organs is ethically acceptable. It is interesting to note that when we first started heart transplantation, the world doubted the ability of the doctor to diagnose the moment of death. The world said that the doctor does not really know when a patient is dead. But we know from experience that in any major hospital, especially during the night, when a nurse doing her rounds comes upon a patient whom she thinks is dead, she will call a doctor; this is usually the houseman, the most junior doctor in the hospital. He will come and determine that the patient is dead using three criteria: there is brain death because there are no reflexes, there is no spontaneous respiration and there is no cardiac activity. On these three criteria, brain death, no spontaneous respiration and no cardiac activity, the doctor will certify the patient dead, and no one will doubt his ability to do so. Once the patient has been certified dead and permission for a post-mortem is obtained, then there is nothing to stop the pathologist from doing a post-mortem immediately, and, if he

feels that the heart is an interesting specimen, he will remove that heart and put it in a bottle to demonstrate its pathology to the students later on. But when a highly qualified team of doctors, using all the means not to make a mistake, having determined death using the same criteria, remove that heart, but instead of putting it in a bottle, they put it into a patient in an attempt to save his life, is the world right in questioning the abilty of these doctors to diagnose the moment of death? That this is an unethical and immoral method? To me the question is not whether it is unethical or immoral to transplant a heart in an attempt to allieviate suffering; to me the question is whether it is moral and ethical to bury that heart so that it can be devoured by worms.

Ladies and gentlemen, I therefore feel that we cannot stop this operation because it is immoral or unethical.

We must ask ourselves further. Why did the heart transplant cause such a tremendous uproar? Could it have been due to the fact that for countless ages the peoples of the world of all races and religions have regarded the heart as the seat of affections and passions, for man as well as beast, and, in the case of man, even as the seat of the soul itself? This age-old mystique enveloping the heart has persisted down to this very day in all classes of society — a mystique enshrined for all nations of the world in their every day thoughts, their sayings, their rituals and their observances. Man in the course of evolution, resulting from his struggle for existence, came to regard the heart as the source of his being and handed down this belief as a social-cultural heritage.

From time immemorial the heart was regarded as the most vital part of the body and the seat or abode of a number of qualities, many of them even of a conflicting nature, such as courage and cowardice, love and hate, generosity and meanness, kindness and cruelty, sincerity and falsehood, and so on. Since the beat of the heart is regarded as a sign of life and its cessation as a mark of death, it is therefore not surprising that the heart in the course of time came to be regarded by all races as the most important organ of the body and the seat of emotional life in all living beings; of love and hate, courage and timidity, hope and despair, lust and desire, joy and grief, and, in the case of men, of belief and disbelief.

The most important influence in the formation of this social-cultural matrix sustaining the mystique of the heart in western civilisation is undoubtedly the Bible. There are numerous references both in the old and in the new testament to the heart and the rôle that it is supposed to play in human thoughts and actions. In fact, of all the internal organs of the body the heart is mentioned 826 times in the bible, whereas the kidneys are mentioned 27 times, the liver 14 times, the secretions of the gall bladder 10 times, the stomach once only and the lungs not at all. It is therefore not surprising that even the physicians of antiquity believed like Hippocrates that the heart coould not be touched for "as soon as the heart is touched immediate death will result".

In a Bradshaw lecture in 1919, Sir Charles Ballance gave a number of delightful references to injuries to the heart mentioned in the classics. He pointed out that many physicians, such as Galen, had made examinations of gladiators and pointed out that when a wound was inflicted to the heart immediate death resulted. In fact, they even pointed out that if the left ventricle was injured, then death was more rapid. But certain people doubted this, amongst them pathologists like Hollerius, Turbi and others, and showed that at post-mortem they found evidence of wounds of the heart in gladiators who had had a history of a chest injury, and they showed that these gladiators had not died from the wounds of the heart. So after 18 centuries people started to doubt the thoughts of Hippocrates that injuries to the heart were always fatal, and they started to investigate this hypothesis in the laboratory, and we have people, such as Becker, Klebs, Cohnheim and Rosenbach, who in the laboratory showed that the heart could be approach-

ed surgically, that wounds could be inflicted to the heart and that these animals will survive. But in spite of the success obtained in laboratory animals, Bilroth, himself not a very timid surgeon, wrote in 1875: "Parancentesis of the pericardium is an operation which in my opinion approaches very closely to that kind of intervention which some surgeons would term a prostitution of the surgical art and others madness". And in 1885 he wrote: "Let no man who hopes to retain the respect of his medical brethren dare to operate on the human heart". In 1896 Paget stated: "Surgery of the heart has probably reached the limit set by nature to all surgery. No new methods and no new discovery can overcome the natural difficulties that attend a wound of the heart". And one year later these predictions, a surgeon by the name of Rehn sutured the beating human heart and the patient recovered.

I think we will all agree that it is not easy to rid ourselves of this so to speak ingrained habit of thought and think rationally of the heart as only a muscular pump, responding now vigorously, now more gently to the needs and demands of the body as life's situations change or fluctuate from time to time, or even from moment to moment. And why should we rid ourselves of these ingrained habits of speech and thought, provided we do not allow them to inhibit our scientific thinking on matters clothed through the ages in garbs of emotional and poetic figures of speech? In spirit we live by utterances only, and myth and legend and symbolism is what we thrive on. For although our little life, in the immortal words of Shakespeare, "is rounded with a sleep", we remain "such stuff as dreams are made of". Let the spirit on the heart of the bible, literature, myth, legend and every-day speech, therefore, remain, so to speak, untouched by the surgeon's knife, but let not our scientific thinking be clouded by these thoughts. And let us, therefore, not condemn the future of heart transplantation as a result of this.

We have asked ourselves if there is a future in heart transplants. We have seen that there are no ethical or moral reasons why the operation should not be performed. When can we say that a procedure has a future? I think that a surgical procedure has a future when we can answer two questions. First when we can say that there is a need for this procedure, and second, when we can say that we can perform this procedure; we are technically able to do this operation and we are capable of looking after the post-operative complications of this operation.

Let us now see if there is any need for heart transplantation. In the last 25 years the world has witnessed a tremendous improvement and increase in the ability of physicians to treat heart disease. They are today able to treat most of the congenital deformities that children are born with; they are able to correct the ravages of rheumatic fever; put in new valves, open up narrow valves; they are now able to correct lesions of the pericardium, and able to operate round the heart correcting a patent ductus arteriosus and co-arctation of the aorta. But in spite of all these advances, little progress has been made in the treatment of diseases affecting the heart muscle, and ,apart from revascularisation operations and the excision of small aneurisms, we are unable to treat the patient once there is failure of the pump. This has become the greatest challenge in the treatment of heart disease, becuse diseases affecting the heart muscle, failure of the pump, is today the most common cause from heart disease. In the United States alone it is estimated that half a million people die every year of one of the conditions affecting the heart muscle; and in the whole world millions of people must die every year from these affections.

As I have just said, the heart is a pump and these diseases affect the pump. How can we then correct them? The only way that we can correct them is to replace the pump, either by means of a mechanical device or by means of a heart transplant, the heart either being taken from a human donor or from an animal donor. With our present knowledge of artificial hearts, it is not yet possible to

use a mechanical heart to replace heart function completely for any length of time. Therefore, in searching for a solution to this immense problem of disease of the heart muscle, it became obvious that, if we wanted to treat our patients today, the only way that it could be done was by a heart transplant. We also realised, as we will see later, that due to our imperfect knowledge of the immunological reactions to a foreign transplanted organ, it would not be possible to use a xenograft, and therefore an animal donor could not be used ,and as such we had to use a human donor.

Let us now see the type of patient that may benefit by the operation. The first indication for heart transplantation in our cases has been mainly ischaemic heart disease. We have so far done 5 heart transplants and two of them were done for ischaemic heart disease; one was done for cardiac myopathy and two transplants were done for rheumatic heart disease. Let us analyse these cases more closely and see whether they really needed this operation.

A study of the haemodynamic findings of the first patient six months before transplant shows that there is an elevation in the right heart pressure because both the right atrial and right ventricular pressure are elevated, indicating that there is failure of the right side of the heart. There was also a marked elevation in the pressures on the left side of the heart, indicating that the left side is also failing, the left atrial pressure being 35mm. of mercury, the endiastolic pressure in the left ventricle being 25-30mm. of mercury. The cardiac index was remarkably reduced to 2.43 litres per minute per meter square, indicating that here we have a patient with total heart failure. And when his heart is examined, it will be seen that the mass of the left ventricular muscle has been destroyed by ischaemic heart disease; instead of the beautiful red muscle which can contract and expel the contents of the left ventricular chamber, the left muscle is is now completely replaced by white fibrous tissue due to the ischaemic death of this muscle. The question that we must ask ourselves is whether we are going to allow this patient to die, or to offer him the hope of further life by means of a heart transplant.

The haemodynamic findings in the second patient also show right heart failure, severe left heart failure and low cardiac output. And when his heart is examined, the left ventricular chamber will be seen grossly dilated as a result of the damage of ischaemic heart disease; the heart muscle is replaced by fibrous tissue. This man was in the terminal stages of heart disease; he was receiving 600mg. Lasex daily; he was short of breath by day and by night, and he had had a pulmonary embolus which nearly killed him about a week before the operation. There is also a localised aneurysm of the left ventricle. And we should ask ourselves: Do we believe that this patient can benefit by a heart transplant?

The third case was a patient suffering from cardiac myopathy. He had been ill for many, many months and had actually had an operation because it was thought that he was suffering from mitral valve disease. His general condition gradually deteriorated and he failed to respond to further medical treatment. Again, one will find total heart failure, both on the right side as well as on the left and a low cardiac index. The patient attempted to commit suicide one day before the transplant, because he thought that life was not worth living any more. If you look at his heart you will see that the left ventricular wall is grossly thickened by this unknown disease; it cannot contract any more and it cannot therefore act as a pump.

The next case was a patient who suffered from aortic valve disease as a result of rheumatic fever. Because of a haemodynamic defect, the aortic valve was replaced, but despite the correction of the valvular lesion, the patient's condition continued to deteriorate and eventually he was in the terminal stages of heart failure. On re-examination, it was found that there was no further defect of the valve, but there was total failure because the heart muscle had been destroyed by

the rheumatic fever. There was severe right heart failure showing a right atrial pressure of 21mm. of mercury, a left atrial pressure of 28mm., an endiastolic pressure of 20-12mm. of mercury, with a cardiac index of 1.2 litres per minute per meter square. The heart after removal showed extensive damage of the muscle both as the result of the rheumatic fever and the long-standing left heart failure.

The last patient was a coloured woman who suffered from mitral incompetence. Her mitral valve was replaced using a pig's xenograft, but despite the haemodynamic correction of the valve lesion, she continued to remain in severe heart failure. Her condition deteriorated and for six months before surgery her cardiac index was diminished to 1.2 litres per minute per meter square.

These are the patients who we believe can benefit by heart transplantation, and therefore, I think that the answer to our first question "Is there a future for this procedure because there is a need for it?" must be in the affirmative, because I do not think that any body can tell me what else we could have done for the patients that I have just described. Thus there is a definite need for replacement of the pump.

I have already dealt with the donors, but I would like to add that a patient can only be used as a heart donor because death is not instantaneous. If the circulation of a patient should stop at this minute, then the brain will die within 3-5 minutes, the liver will probably die or have irreparable damage within $\frac{1}{2}$-1 hour, the kidneys will probably be damaged so that they will not function adequately within 2-3 hours. The heart will tolerate anoxia extremely well and could probably be transplanted $2\frac{1}{2}$-3 hours after the circulation has stopped. It is interesting to note that the nails and hair will only die six days later. It is for this reason that we can use a human donor that has been certified dead. We can actually wait until the heart stops beating and there is a possibility that this heart will start functioning adequately after it is transplanted.

I have said that we consider a patient is dead using three criteria. However, you will agree that a patient is really dead when his brain is dead, and if his doctors can prove brain death without a shadow of a doubt, then there is no reason why the heart cannot be removed for transplantation while it is still beating. Let me explain this further, because this is some thing that has not been properly understood both by doctors and by the lay publis. If I could have a human being that has just been hanged where there is brain death due to the hanging, I could re-start his heart immediately, or, if his heart is still beating, I could continue that heart beat by ventilating artificially for this patient, and I could probably keep that heart beating for a week by means of artificial ventilation. But you will all agree with me that the person cannot return to life because his brain has been killed by the hanging. Therefore, why should one wait until the heart stops beating? There is no sense in this reasoning because there is no further hope of life for the patient. There is no reason why a beating heart cannot be removed, especially when one remembers that once brain death has been declared, responsibility does not lie towards the donor any more. We have a responsibility then towards the recipient and one must do everything in one's power to give that patient the best chance of survival, and if his best chance of survival is by removing a beating heart, then this can be done.

Once a donor has been given to the transplant team, then the patient and donor are prepared, and they are moved into adjoining operating rooms. I have mentioned that the heart will only die gradually and that it will probably take between 2-3 hours before it is really dead. We would like to prevent this gradual death, and we would like to prevent as much as possible the damage of ischaemia to that heart, and therefore we take certain precautions, such as either to cool the heart down to diminish its metabolic demands, or to perfuse the heart with oxygenated blood, or to cool it down and perfuse it with oxygenated blood. We prefer to protect the heart from ischaemic death, after the donor has been declared

dead, by perfusing it with oxygenated blood and by cooling it down. And this is done as follows: The donor and patient are moved into adjoining operating rooms; both the donor and the patient's chests are opened by a median sternotomy which runs down the middle of the chest and the sternum is cut in half. As soon as the donor's heart is exposed, it is connected to a heart-lung machine to supply it with oxygenated blood. This is done very simply by cannulating the right atrium for venous drainage, passing the blood through the heart-lung machine and pumping it back into the arterial system by means of a catheter inserted into the ascending aorta. If other organs, such as the liver and kidneys, are also being used for transplantation, then total body perfusion is continued, but if only the heart is going to be used, then a clamp is applied to the ascending aorta distal to the arterial catheter; the flow is reduced to about 400mm. per minute and only the heart is perfused. Once the heart has been perfused for 20 minutes and cooled down to about 20°C, perfusion is stopped and the heart is excised as follows: The superior vena cava is ligated and divided distal to the ligature; the aorta is divided more or less where the ascending aorta joins the arch; the right and left pulmonary arteries are divided, as well as the four pulmonary veins. Care is taken not to damage the pace-maker or sinoauricular node that lies in the area of the superior vena cava, and therefore we do not cut where the superior vena cava enters the right atrium. The heart is then completely removed, and we are left with an empty pericardial sac, the stump of the aorta, the openings of the pulmonary arteries and veins and the inferior vena cava. The heart is transported to the operating theatre of the patient. At this stage it has already been determined that the donor's heart is normal, and the patient is connected to the patient's heart-lung machine by joining the catheter that has been left in the ascending aorta to the arterial line of the heart-lung machine of the patient and applying a clamp distal to the entrance of this catheter. Because the aortic valve is competent and the catheter supply has a high pressure in that section of the aorta, it will perfuse the coronaries. I would like you to notice that the whole heart is removed for transplantation: the whole of the right atrium, the whole of the left atrium, both ventricles, the pulmonary artery and its bifurcation and a good length of aorta.

The patient is connected to the heart-lung machine by draining the venous blood through two vena cava catheters and returning the arterialised blood from the oxygenator through a catheter placed either in the ascending aorta or in the femoral artery. During this operation, while the heart is removed and the new heart transplanted, the heart-lung machine will supply oxygenated blood to the body and keep it alive.

Once the patient's heart has been excluded from the circulation with a heart-lung machine, it is also removed by applying a clamp to the ascending aorta, proximal to the catheter, then dividing the aorta, close to the coronary ostia, dividing the pulmonary artery on the pulmonary valves and then detaching the ventricles from the atria. What remains in the patient, therefore, using this technique, are the two venae cavae catheters in the right atrium draining the venous blood and the arterial catheter in the aorta supplying oxygenated blood. A section of the right atrium and intra-atrial septum is left behind, as well as a section of the left atrium; the aorta and a pulmonary artery with the two branches are also left behind. The new heart is now connected to the remnants that have been left. But before this can be done, the new heart has to be prepared for transplantation by dissecting between the aorta and pulmonary artery so that there will be more mobility of these two vessels. The bridge which forms the bifurcation of the pulmonary artery is also excised. This bifurcation is used because as a rule the patient has big, dilated pulmonary arteries while the donor has a smaller normal pulmonary artery; therefore, there is a disparity in size which makes it difficult to anastomose. If the bifurcation is used, there is a bigger opening and the disparity will be less. In

addition the atria have also to be prepared for transplantation for connection to the remnants that have been left behind in the patient. The back wall of the atrium is opened and the holes thus made are connected to the remnants that have been left behind. To ensure that there will be sinus rhythm, care is taken not to injure the area where the superior vena cava enters the right atrium. The back wall of the left atrium is opened by excising that piece of muscle between the entrance of the four pulmonary veins. We now have a hole in the back of the right atrium, a hole in the back of the left atrium, the aorta and the pulmonary arteries which must be anastomosed. I would like you to note that great care has been taken not to injure the sino-auricular node, and, by cutting into the intra-atrial septum, the atrio-ventricular node will not be injured. With this technique, therefore, one can be certain that the transplanted heart will start in sinus rhythm without any conduction defect and no heart block. It is not difficult to anastomose the opening in the back wall of the left atrium to the left atrium by using the left wall and the intra-atrial septum and anastomosing the opening in the back wall of the right atrium using the remnant of the right atrium and again the intra-atrial septum. The pulmonary arteries and the aorta are also anastomosed.

During this whole procedure the donor heart is supplied through the catheter in the ascending aorta with oxygenated blood so that there will be no further ischaemic damage, and the patient's body is likewise oxygenated through the catheter in the ascending aorta.

The operation is now complete.

It can now be seen that the systemic venous blood will return into a small section of the patient's original atrium, then flow through the anastomotic opening into the donor's right atrium and then into the right ventricle. The same applies for the pulmonary venous blood.

At this stage the clamps are removed from the aorta, the heart is rewarmed and it is usual for it to start in spontaneous sinus rhythm, if it has been well protected. If it does not, it can be defibrillated by an electric shock.

When the heart is in place, it will be seen to lie in a fairly large pericardial sac, because the latter has been dilated as the result of the disease.

I would like to point out that the cardiac output of the donor heart before it was removed was 6.9 litres per minute, while the patient's cardiac output was 2.5 litres per minute. After transplantation, the donor heart had a cardiac output of 6.0 litres per minute, nearly the same as before transplantation, indicating that immediately after transplantation, the heart can supply an adequate output. With this technique it is also possible to have the patient in sinus rhythm. This is important because one of the signs of rejection is a change in the electrocardiogram, such as arhythmias and heart block, and with this technique one can be certain that these changes are not due to the surgery.

It can therefore be seen that technically this operation is possible, and in the transplant experience of the world, one will find very few techincal failures. But this is not all that is necessary to make a transplant successful because, as I have pointed out, the body has the ability to detect this foreign organ that has been transplanted. The body has the ability to distinguish between self and non-self, and as soon as it recognises that the transplanted organ is foreign to it, it will set up immunological reactions against it. Substances liberated by the transplanted organ, the antigens, will be detected by the immunologically competent cells, which will change and produce antibodies which will circulate back to the transplanted organ and destroy it.

However we have the ability to suppress the central mechanism that reacts to the antigen by slowing down the amount of antibodies that are liberated to destroy the transplanted organ. Unfortunately this is not specific for the transplanted organ; it suppresses the whole body's ability to react to foreign substances. Therefore it will also suppress the body's ability to react to infection. Thus in deciding on the immuno-suppres-

sive drugs that are to be used, and on the dosage, one is in great difficulty, because enough has to be given to prevent rejection while at the same time the dose must not be such as to increase the liability to infection. And this is the problem that we have today, to use enough of the immunosuppressive agents to prevent rejection but stilll allow the body its ability to react to infection. We therefore aim at keeping the drugs at a low level, and it is only when rejection become clinically evident that we increase the dosage to slow down the rejection process.

Our problem has been how to detect rejection in the transplanted heart. I think that rejection can be compared to an infection, and we can diagnose rejection using the same groups of symptoms that appear in infection or inflammation. As in inflammation one will thus find systemic changes, such as a rise in temperature, increase in pulse rate, anorexia, malaise and occasionally mental changes. Likewise, as in inflammation, in rejection one will find local changes, an enlargement of the transplanted organ, deterioration in function and, if the rejection is well advanced, one may find evidence of parenchymal destruction, and lastly, one finds other changes which may not really be part of the rejection episode but are associated with it. So other immunological changes may be present.

Let us now see how all these factors have helped us to diagnose rejction in the transplanted heart:

Systemic changes: In one case there was an episode of rejection about 20 days after surgery. There was a rise in temperature, a rise in pulse rate and a rise in respiratory rate. The dose of the immunosuppressive drugs was increased and this was soon accompanied by a drop in temperature, pulse rate and respiratory rate. The sedimentation rate was also raised showing systemic activity as rejection occurs, but when the latter was treated, there was a drop in the sedimentation rate.

So systemic changes can be looked for and these can help us to diagnose the onset of rejection. These changes will serve as a warning to step up the immunosuppressive drugs in order to slow down the rejection episode again.

Local changes: These consist in enlargement of the heart during the rejection episode. This enlargement is not so much due to a swelling of the heart muscle, but mainly to a dilatation of the heart during rejection. It can be detected by the onset of a gallop-rhythm and a functional mitral systolic murmur. There is also a pericardial reaction during rejection and a part of the enlargement is due to a percardial effusion.

One would expect that when the heart muscle is damaged due to rejection there will be liberation of enzymes which could help in the diagnosis of rejection. Unfortunately this has not proved to be of much value because we have not been able to find evidence of a rise in the enzyme levels during an episode of rejection. This is difficult to explain, but we believe that enzyme changes occur late in rejection. If rejection is diagnosed and treated early, then enzyme changes do not occur. However, it is interesting to note that one gets a certain rise in the enzyme level after the rejection has been reversed, and this is probably due to the increase in the immuno-suppressive drugs which cause a certain amount of liver damage.

Functional changes: One would imagine that if the heart is invaded by cells and oedema occurs, functional changes will manifest themselves. This can be detected at the bedside by the onset of right heart failure, a rise in venous pressure, enlargement of the liver, dilatation of the heart as shown by a gallop rhythm and the onset of a systolic murmur. But in most cases the earliest indication of a disturbance in the heart function is a change in the electrocardiogram. Changes, such as arhythmias and conduction disturbances, may be present, but the most important is a drop in the voltage of the electrocardiogram. When the rejection is treated, the voltage returns. In fact, we belive that this is the earliest and most important sign of rejection and we will treat a patient for rejection if there is

only a drop in voltage of the electrocardiogram.

We have investigated other immunological changes, such as the development of heterophile antibodies, of cytotoxic antibodies and so on, but we have not found these changes of any value in the early diagnosis of rejection.

To sum up, we have been able to detect rejection of the transplanted heart early by observing the voltage of the electrocardiogram, and then usually the rejection can be reversed by increasing the immuno-suppressive drugs.

Despite our ability to diagnose rejection and despite our ability to reverse a clinically evident rejection episode, rejection, as I stated in the beginning, takes place all the time and the heart will eventually be killed by these episodes. When the heart of Dr. Blaiberg was removed at postmortem, we found very little evidence of rejection in the mitral valve; the heart muscle also looked fairly normal and there was little change in the coelium of the atrium. But the transplanted aorta, which was normal during the transplant, showed extensive atherosclerotic changes and it must be remembered that the patient's original disease was atherosclerosis. The coronaries were also thickened from the deposition of cholesterol and the vessels extremely narrowed. This is due to a combination of the rejection damage and the deposition of cholesterol. In other words, rejection after 19 months had caused so much vascular damage that the patient again developed ischaemic heart disease, that the heart muscle was again destroyed by the original process that had caused the illness in his first heart.

I have shown that there is an indication for heart transplantation. I have shown that we have the ability to diagnose rejection and to reverse it. But I have also shown that at the end the transplanted heart will be destroyed. But in series of slides I can show you a patient 12 days after surgery, a man who was dying from heart disease, was short of breath by day and night and could not eat because his liver was so congested. And then you can see him normal, without any symptoms of heart disease only 12 days after the heart had been transplanted.

Another shows a man who 18 days after transplantation was able to shave himself again when for 6 months before surgery he could not do so because he had been so ill. Our slide shows him celebrating the New Year, when I am quite certain that without the transplant he would have been dead or at the most bedridden. Another shows him able to enjoy a sport that he had loved all his life — fishing. And another one shows him celebrating with another transplant patient the first anniversary of his own transplant.

Yet another slide shows a patient who was dying from heart disease, who attempted to commit suicide one day before the transplant, now able to play tennis again.

I think, ladies and gentlemen, it would be better if I were to ask you whether there is a future in heart transplantation. Or perhaps it would bet better if we ask these patients if there is a future in heart transplantation? I agree that we have a number of difficulties and we are far from solving the many problems. But is transplantation worthwihle? Is there a future to it? Are we able to solve the problems that lie ahead?

We have so far done 5 heart transplantations. One patient lived for 18 days, one for 593 days, one is alive and well 365 days after transplant, one died 64 days after transplant and one is alive and well 143 days after transplant. The average life expectancy of these patients if a transplant had not been done would have been 30 days. So do you think there is a future in heart transplantation? Do you think that we are going to solve the problems that lie ahead? I think that it is all in the state of the mind:

If you think you are beaten, you are,
If you think you dare not, you don't
If you think you'd like to win but can't,
Its almost a cinch you won't.
If you think you'll lose, you've lost,
For out in the world you'll find
Success begins with a fellow's will;
It's all in the state of the mind.

For many a race is lost ere ever a race is run,
And many a one fails ere ever his work is begun;
Think big and your deeds will grow,
Think small and you'll fall behind.
Think that you can, and you will;
It's all in the state of the mind.

If you think you're outclassed, you are,
You've got to think hard to rise,
You've got to be sure of yourself
Before you ever can win a prize.
Life's battle does not always go
To the stronger or faster man,
But sooner or later the man who wins
Is the fellow who thinks he can.

Thank you.

VARIANTS OF HAEMOGLOBIN F AND OBSERVATIONS ON HAEMOGLOBIN F (MALTA)

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Introduction

The major haemoglobin component found in the blood of humans at birth is foetal haemoglobin, haemoglobin F. In common with most other human haemoglobins it has a tetrameric structure, each molecule being made up of two different pairs of polypeptide chains. In the case of haemoglobin F these are the α-chains and the γ-chains, and haemoglobin F thus has the molecular formula $\alpha_2 \gamma_2$. Whereas the α-chains are common to the major adult haemoglobin component, haemoglobin A, to the minor adult haemoglobin component, haemoglobin A_2, and to the embryonic haemoglobin Gower-II, the γ-chains are unique to haemoglobin F. At birth haemoglobin F accounts for 60-80% of the haemoglobin present in the blood. The other haemoglobins present at birth are haemoglobin A ($\alpha_2 \beta_2$) which accounts for 20-40% of the haemoglobin and a very small amount of haemoglobin A_2 ($\alpha_2 \delta_2$), less than 0.5%. As a child matures, the level of haemoglobin F in the blood decreases until, by the age of 3-6 months ,it is less than 5%. The majority of the rest of the haemoglobin is then haemoglobin A, but there is also an increased amount of haemoglobin A_2 (2-3%).

Because haemoglobin F consists of two types of polypeptide chains, two classes of haemoglobin F variants are possible, those possessing abnormal α-chains and those with abnormal γ-chains.

Alpha chain variants

Because the α-chains are common to both haemoglobins A and F, any child inheriting an α-chain mutation will have four main haemoglobin components present at birth, haemoglobin A ($\alpha_2\ \beta_2$), haemoglobin F ($\alpha_2\ \gamma_2$) and the corresponding variants, haemoglobins A^x ($\alpha_2{}^x\ \beta_2$) and F^x ($\alpha_2{}^x\ \gamma_2$). This has been observed, for example, in the case of an infant with the α-chain variant, haemoglobin G Philadelphia (Minnich *et al.*, 1962, and Weatherall and Baglioni, 1962). Both the foetal haemoglobins disappear as the baby matures and in the adult blood there will be present haemoglobin A, haemoglobin A^x, haemoglobin A_2, and the α-variant of haemoglobin $A_2{}^x$. Observations such as this have made it appear likely that a single gene controls α-chain synthesis both in foetal and in adult life.

Gamma chain variants

Relatively few γ-chain variants have been described so far and in those that have been found, the amino acid substitution appears to have little effect on the function of the haemoglobin molecule. Because there are so few γ-chain variants known it is possible to discuss each one separately. It should be noted, however, that not all of them have been fully characterized so that it is possible that two haemoglobins discussed under separate headings are in fact the same variant. Their electrophoretic mobilities have in general been expressed relative to haemoglobin A and its two common variants haemoglobin S and haemoglobin C. The order of increasing anodic mobility of these haemoglobins at alkaline pH is C,S,A. Normal foetal haemoglobin, haemoglobin F, has a slightly lower mobility than haemoglobin A.

(i) *Haemoglobin F-Texas I*

This variant was observed during a survey of cord blood carried out in Britain (Jenkins *et al.*, 1967). In electrophoresis at alkaline pH a haemoglobin component with a slower mobility than haemoglobin C was found in a healthy, full-term female child of West Indian parentage. The variant was absent in the parents and had the typical foetal haemoglobin properties of resistance to denaturation by alkali and the presence of tryptophan "notch" in the absorption spectrum at 289-290 nm. The amount of this haemoglobin diminished in the first few months of life and peptide patterns of tryptic digests showed that the substitution was lysine for glutamic acid in position 5 of the γ-chain. Only one case of this variant was found.

(ii) *Haemoglobin F-Texas II*

This variant, which may be the same as haemoglobin F-Texas I, was found in the United States of America in the cord blood of five Negro infants (three of them siblings) and one Caucasian infant (Schneider *et al.*, 1964; Schneider and Jones, 1965). All the babies were born at term and appeared healthy, the abnormal haemoglobin making up 12% or less of the total haemoglobin. The total foetal haemoglobin values as determined by alkali denaturation were in the range 68-82%. At six months the variant was barely detectable in the infants. In the initial reports haemoglobin F-Texas II was not observed in the parents but later (Schneider *et al.*, 1966) it was found that a trace component with the electrophoretic mobility of haemoglobin F-Texas II was in fact present in the blood of the father of the three sibs. In electrophoresis in an alkaline buffer, haemoglobin F-Texas II had a lower anodic mobility than haemoglobin C. It behaved in the same way as normal haemoglobin F in immunodiffusion but hybridisation studies did indicate that an alteration in structure had occurred in the γ-chain. This alteration did not affect the characteristic tryptophan fine structure band in the spectrum at 289-290 nm. Peptide analyses by column chromatography of tryptic hydrolysates of the variant were carried out by Schneider and Jones (1965), and the results indicated that one of the glutamic acid residues at positions 5 and 6 of the γ-chain had been substituted by lysine.

(iii) *Haemoglobin F-Roma*

One case of this variant has been observed in a healthy, female child born to parents in Rome (Silvestroni and Bianco, 1963). This haemoglobin which had an electrophoretic mobility at alkaline pH greater than that of haemoglobin F was resistant to denaturation by alkali. However, the tryptophan absorption at 289-290 nm was apparently very slightly increased as compared with that of haemoglobin F. Not enough material was available to work out the substitution but it was differentiated from haemoglobin Bart's (γ_4) which has a similar electrophoretic mobility at alkaline pH, and hybridisation experiments showed that the change had taken place in the γ-chains. Silvestroni and Bianco (1963) were also able to measure the relative percentages of haemoglobin F Roma and the total foetal haemoglobin (determined by alkali denaturation) as the child matures *(Table 1)*.

TABLE I

Relative rates of disappearance of haemoglobin F-Roma and total foetal haemoglobin (from Silvestroni and Bianco 1963)

	F-Roma (per cent of total Hb)	Total foetal Hb (per cent of total Hb)	F-Roma (per cent of total foetal Hb)
newborn	17.0	79.0	21.5
45 days	12.0	37.0	32.5
3 months	5.82	18.0	32.3
5 months	0	3.5	-

(iv) *Haemoglobin F-Warren (F-Houston)*

This variant was first found in the cord blood of a healthy Negro newborn by Huisman *et al.* (1965) who called it haemoglobin F-Warren. Electrophoretically, its mobility was between that of haemoglobins S and C at an alkaline pH. An apparently identical haemoglobin was reported by Schneider *et al.* (1966) who gave it the name of haemoglobin F-Houston. In both cases the haemoglobin amounted to 13-15% of the total haemoglobin at birth and had declined to low levels by four months. In their one infant Huisman *et al.* (1965) were able to measure the relative rates of disappearance of haemoglobins F-Warren and F and found that as the child matured the level of F-Warren fell more slowly than that of F *(Table II)*. No clinical or haematological abnormalities were apparent due to the presence of this variant which was antigenically and spectrally indistinguishable from haemoglobin F. Hybridisation showed that it was a γ-chain mutant. It is interesting that both

TABLE II

Relative rates of disappearance of haemoglobin F-Warren and total foetal haemoglobin (from Huisman et al., 1965)

	F-Warren (per cent of total Hb)	Total foetal Hb (per cent of total Hb)	F. Warren (per cent of total foetal Hb)
newborn	13.2	94	14.1
6 weeks	13.7	78	17.6
10 weeks	10.0	48	20.8
16 weeks	4.9	16	30.6

groups of workers reported relatives, in the case of Huisman *et al.* (1965), a brother and sister, in the case of Schneider *et al.* (1966), the father, with very small amounts of a band with electrophoretic mobility similar to the foetal haemoglobin variant. A change of glutamic acid to alanine has been suggested for this variant by Schneider *et al.* (1966), but purely on the basis of the relative amino acid compositions of haemoglobins F and F-Warren.

(v) *Haemoglobin F-Hull*

Three cases of this variant were found in two unrelated families in Kingston-upon-Hull, England (Sacker *et al.*, 1967). In one family an otherwise normal, healthy baby had 14% of the variant at birth. A second child born to the same parents had 9% at birth but was born prematurely and died. The third case, like the first, was a healthy baby with 7% of the variant. This

variant was not observed again during a survey of 12,000 cord bloods in Britain (Sacker *et al.*, 1967). It was not found in the parents and the amounts in the children declined during the first four months of life. Spectrally it showed a typical tryptophan "notch" at 289-290 nm. On paper electrophoresis at pH 8.9, its anodic mobility was less than that of haemoglobin C, suggesting again the change of an acidic to a basic amino acid. This was confirmed by the peptide maps of tryptic digests of the haemoglobin which showed that glutamic acid at position 121 of the γ-chain had been altered to lysine.

(vi) *Haemoglobin F-Alexandra*

This variant has not been well characterised so it may be the same as one of the others reported. One case was found by Fessas *et al.* (1959) in Greece, and an apparently similar component was reported by Vella *et al.* (1959) in Singapore. The variant of Fessas *et al.* (1959) had an electrophoretic mobility at alkaline pH between haemoglobins S and C but had the same mobility as haemoglobins S at pH 6.7. At birth the variant amounted to 18.3% of the total haemoglobin compared with a total alkali-resistant haemoglobin level of 60%. Over a period of fifteen weeks the amount of haemoglobin F-Alexandra declined from 18.3 to 2.2% and the total foetal haemoglobin from 60% to 6% (F-Alexandra was thus 30.5% of the total foetal haemoglobin at birth and 36.6% at the age of fifteen weeks). No clinical or haematological abnormality was observed in the child and the variant was absent in the mother. It showed typical foetal haemoglobin properties, the rate of alkali denaturation being the same as normal haemoglobin F and the ultraviolet spectrum showing a marked tryptophan "notch". The variant of Vella *et al.*, (1959) was found in a Chinese baby and amounted to 15% of the haemoglobin at birth. It had the same electrophoretic mobility and the same spectrum as the component of Fessas *et al.* (1959). Again both parents were normal.

(vii) *Haemoglobin F-Malta*

This is the most recent variant discovered and is of special interest to Malta as it is only here that it has been reported (Cauchi *et al.*, 1969). Haemoglobin F-Malta is unique among the foetal variants in that it has a very high incidence, being present at birth in the blood of one Maltese child in every fifty. Electrophoretically, it migrates more slowly than haemoglobin F but more rapidly than haemoglobin S at an alkaline pH and has the same mobility as haemoglobin F at pH 7.0. Haemoglobin F-Malta is also readily separated from normal haemoglobin F on isoelectric focussing in a pH gradient (Brown and Grech, unpublished observations), and with this technique has an isoelectric point at pH 7.44 as compared with 7.22 for normal haemoglobin F. These observations are in qualitative agreement with the amino acid substitution which has been shown to be a change of histidine to arginine at position 117 of the γ-chain (Cauchi *et al.*, 1969). The ultraviolet spectrum of haemoglobin F Malta is identical in the 289-290 nm region with that of haemoglobin F and the rates of denaturation of the two haemoglobins by alkali are very similar (Brown and Grech, unpublished observations).

The variant disappears as the baby matures, in common with other foetal haemoglobin variants, and has not been observed in any parents. Infants born with haemoglobin F-Malta are apparently healthy and have no other haematological anomalies.

Cauchi *et al.* (1969), in a quantitative examination of twelve cases reported that at birth the proportion of the abnormal component ranged from 14.8–22.5% of the total haemoglobin or 20.3–27.4% of the total foetal haemoglobin. To date we have found 47 cases of haemoglobin F-Malta and have quantitated the levels of total foetal haemoglobin, as measured by the alkali denaturation method of Jonxis and Visser (1956), and the amounts of haemoglobin F-Malta, as measured after cellulose acetate electrophoresis by the method of Marengo-Rowe, (1965). Our

values for haemoglobin F-Malta at birth range from 17.7–27.9% of the total haemoglobin or 27.6–37.1% of the total foetal haemoglobin. Thus our values are substantially higher than those of Cauchi *et al.* (1969).

We are studying the relative rates of disappearance of the haemoglobins F-Malta and F as the infants mature. Because of the high incidence of haemoglobin F-Malta it is possible to carry out a much more comprehensive study on the relative rates of disappearance than it is in the case of other foetal variants. Our results to date are shown in *Table III*. The post-natal samples were all obtained from different infants at varying periods after birth. For convenience the results have been grouped into ten day periods as shown in *Table III*. It seems quite clear that the amounts of haemoglobin F-Malta and haemoglobin F are declining at the same relative rate, at least in the first 3 months of life.

We believe observations such as these to be important. It has very recently become apparent that the genetics of γ-chain formation are much more complicated than was formerly thought. Thus Schroeder *et al.* (1968) have shown that at birth, normal human foetal haemoglobin consists of two components which cannot be separated by electrophoresis or chromatography but which differ in having either glycine or alanine in position 136 of the γ-chain. Quantitatively they found that the foetal haemoglobin of newly born infants had three times as many γ-chains with glycine at position 136 as with alanine at position 136. From this and other evidence it now appears likely that there are multiple non-allelic structural genes for the human γ-chain. Schroeder *et al.* (1968) drew up a genetic model in which there were four γ-chain loci on the relevant chromosome, three directing synthesis of γ-chains with glycine at position 136 and one directing synthesis of γ-chains with alanine at position 136. According to this model, γ-chain variants should have either alanine or glycin at position 136 of the aberrant γ-chain and they should amount to about 12.5% of the total foetal haemoglobin. Schroeder *et al.* (1968) in further cases of newborns with haemoglobin F-Texas II and haemoglobin

TABLE III

Relative rates of disappearance of haemoglobin F-Malta and haemoglobin F.

Days after Birth	No. of Observations	F-Malta (per cent of total Hb)	Total foetal Hb (per cent of total Hb)	F-Malta (per cent of total foetal Hb)
0	46	22.9 ± 2.7 (S.D.) (range 17.7 - 27.9)	70.2 ± 9.0 (S.D.) (range 51.5 - 89.5)	32.8 ± 2.3 (S.D.) (27.6 - 37.1)
1-10	-	-	-	-
11-20	3	18.6	56.3	33.7
21-30	1	15.4	42.5	36.2
31-40	2	18.1	51.8	34.9
41-50	4	14.0	46.9	29.6
51-60	2	11.5	33.8	34.0
61-70	2	11.3	40.2	29.7
71-80	1	6.3	19.5	32.3
101-110	1	2.4	9.2	26.1

F-Warren showed that the model predicted correctly the amounts of haemoglobin F-Texas II, which has only alanine in position 136, (12.2% of total foetal haemoglobin in one case) and haemoglobin F-Warren, which has only glycine at position 136, (13.5% and 12.8% of the total foetal haemoglobin in two cases). However, it is inadequate for explaining the quantitative relationships between haemoglobin F-Malta (glycine in position 136 of the γ-chain) and haemoglobin F and also between haemoglobin F-Roma and haemoglobin F (see *Table I* and *Table III*).

The situation has been further complicated by the observations of Schroeder and Huisman (1970) on the haemoglobin F of infants studied from birth to the age of several months. They have found that the ratio of γ-chains with glycine at position 136 to γ-chains with alanine at position 136 changes from 3 : 1 at birth to 2 : 3 after 150 days. The latter ratio was very close to the values obtained for the glycine: alanine ratios in haemoglobin F isolated from normal adults. However, the preliminary observations on the relative rates of decline of haemoglobin F-Warren and haemoglobin F *(Table II)* and of haemoglobin F-Malta and haemoglobin F *(Table III)* are not in accord with this change in ratio. Both variants have glycine at position 136 of the γ-chain and so might be expected to decline more rapidly than haemoglobin F. This does not happen. It is interesting too to mention that Schroeder and Huisman (1970) have found the condition of hereditary persistence of foetal haemoglobin to be very heterogeneous at the molecular level in that they could classify patients with this condition into groups whose haemoglobin F γ-chains contained either only glycine or only alanine, or both, at position 136. This grouping did not depend on the level of haemoglobin F in the blood. It is thus not possible at this stage to draw up a comprehensive genetic model to explain the inheritance and the control of formation of γ-chains, but these observations of Schroeder and Huisman (1970) do increase the importance of the study of foetal haemoglobin variants and their rates of disappearance for the fuller understanding of γ-chain genetics.

A note of caution must, however, enter into any discussion of the genetics of foetal haemoglobin variants. The relative levels of haemoglobin F and haemoglobin F variants in blood not only depend on their relative rates of formation but also of course on their relative rates of destruction. We have here in fact a system where the rate of removal of the foetal haemoglobins from the blood is exceeding their rate of synthesis. Moreover, haemoglobin F and haemoglobin F variants need not necessarily be either formed or destroyed at the same rate as each other.

Acknowledgements

We thank Professor W. H. Bannister and Professor A. P. Camilleri for encouragement and provision of laboratory facilities; Dr. M. D. Falzon for help in the collection of post-natal blood samples; and Mr. M. Falzon for technical assistance.

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HEREDITARY DIAPHORASE DEFICIENCY METHAEMOGLOBINAEMIA IN MALTESE FAMILIES

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Summary

Hereditary Diaphorase Deficiency Methaemoglobinaemia was discovered in seven persons belonging to four Maltese families. These are the first families of diaphorase deficiency methaemoglobinaemia to be recorded from the Maltese Islands. It is suggested that the gene frequency for this type of congenital methaemoglobinaemia is high in the Maltese Islands and that wider systematic surveys would reveal many more cases.

Methaemoglobin (ferrihaemoglobin) normally constitutes only 1% of the total haemoglobin of the red cells. Its presence in a greater concentration is pathological and may be due to a number of different causes, congenital or acquired. The congenital forms are rare and are of two types which are completely different from one another. One type, inherited recessively, is due to an enzyme deficiency in the red cell, (Gibson, 1948), while the other type, showing dominant inheritance, is due to a defect in the globin moiety of the haemoglobin molecule (Horlein and Weber, 1948).

Seven affected individuals in four Maltese families with methaemoglobinaemia secondary to deficiency of the enzyme diaphorase have been discovered in the Maltese Islands and will be described in this paper.

Methods

Methaemoglobin estimation was carried out using the method of Evelyn and Malloy (1938) as described by Varley (1967).

Diaphorase Activity in the red cell was estimated by the method described by Scott (1960). Levels of diaphorase (measured as units of change in optical density per minute $\times 10^4$) below 100 are usually taken as characteristic of the methaemoglobinaemic homozygote, while levels between 100 and 300 represent the heterozygote. Levels in excess of 300 represent the normal state.

Haemoglobin F Estimation: The degree of denaturation of cyanmethaemoglobin was determined using the modification of Bethke, Marti and Schlicht.

G-6 PD Estimation: The Brilliant Cresyl Blue dye test (Motulsky and Kampbell-Kraut, 1964) was used.

Haemoglobin estimation, blood smears and reticulocyte counts were performed by standard methods. PCV was determined using a microhematocrit technique.

Case Reports

Family A. None of our patients had been taking any analgesics or any other drugs. The father and the mother are apparently healthy, look normal and are not related to one another. They hail from an inland village in Gozo, the sister island of Malta. There are six offsprings from the marriage of whom two have been affected.

Case 1. The eldest sibling, a 16 year old male (J.V.) was noted to have had a cyanotic tinge since early childhood, and had been seen by various specialists who had not found any cardiac or pulmonary abnormalities. Intelligence is average and his only complaints have been occasional dizzy spells. When seen by one of us (L.V.), the patient had just undergone an emergency appendicectomy, and had caused some concern to the anaesthetist as the blood oozing at operation was unduly dark. Physical examination revealed no other abnormality. His Hb level was 13.6 g., PCV 40%, MCHC 34, reticulocyte count 0.5%, G6PD activity 50, and Hb F 0.32%. His methaemoglobin level was 10.5% (1.43Gm). His diaphorase level was 109. (Control 350).

Case 2. T.V., the youngest child of the marriage (d.o.b. 4.5.65) was noted to be cyanosed on the day of birth. Cyanosis persisted. There were otherwise no other abnormalities. At the age of nine months, he was seen by a specialist because of the worrying cyanosis, but no physical abnormalities were found. His lungs and heart, in particular, were thought to be normal. Apetite, developmental milestones, both mentally and physically appeared normal. At the age of 3, he developed peritonitis from a perforated appendix. He died a few days after an emergency laparatomy. During his terminal illness, intravenous ascorbic acid, 500 mg daily was given. Investigation results (taken when he was still healthy) were as follows: Hb level 13.2 g; PCV 44%; MCHC 30; reticulocyte count 1%; G6PD activity 50; Hb F 0.9%. His methaemoglobin level was 8.3% (1.07Gm). His diaphorase level was only 47. (Control 350).

Family B. The mother of this family is dead. The marriage is not consanguineous. There were eight sublings from this marriage, and two are affected.

Case 3. The eldest sibling (J.V.) a thirty year old male, was the most cyanosed member of the family. His only complaints have been dizzy spells especially after exertion. Cardiac and pulmonary disease have been excluded on medical examination. He works as a heavy manual labourer. He has emigrated to Australia, and investigations to prove the presence of methaemoglobinaemia secondary to diaphorase deficiency have unfortunately not been carried out. He has presumed diaphorase deficiency because the deficiency in his sister has been proved.

Case 4. (S.S., a 27 year old female, now married, is the third child of the marriage. She has always been noted to be moderately cyanotic, but less so than her elder brother (Case 3). Her health has always been good but she has been examined by specialists in the past, as her

parents were afraid there was serious underlying disease. The cyanosis had become especially marked when she was pregnant. The pregnancy was otherwise uneventful. The cyanosis diminished after pregnancy only to become more marked when she was again pregnant. She has now two children who appear normal. Her Hb level was 14.2g; PCV 43%; MCHC 33%; reticulolocyte count 0.1%; G6PD activity 50; Hb F 1.4%. Her methaemoglobin level is 16.6% (2.35g). Her diaphorase level is 0. (Control over 400)

Family C. There are ten siblings from this union, which is not consanguineous. Only one child is affected.

Case 5. (R.V.), a fourteen year old girl is the fifth child of this family. She is of normal height and development. Her intelligence is average. She is symptomless. There are no physical abnormalities apart from the presence of a mild cyanotic or lavender hue. Her Hb level is 1218/g; PCV 41%; MCHC 31%; reticulocyte count 0.6%; G6PD activity 50; Hb F 0.7%. Her methaemoglobin level is 22.5% (2.82g). Her diaphorase level was 5. (Control 290).

Family D. The father and mother are unrelated though both hail from the same town in Malta. There are ten siblings in the family of whom two are affected.

Case 6. Y.B., is a 26 year old female. She is the eldest offspring. She had been noted by her parents to have had mild intermittent cyanosis when she was a child and again when she was pregnant. She is otherwise perfectly normal, and has a three year old son. Her methaemoglobin level is 6.2% (0.81g.). Her diaphorase level was 0. (Control 290)

Case 7. The condition had been recognised in N.B. the fifth child now 19 years old, because of the colour of her blood at appendicectomy. Diaphorase levels were not estimated then. She had never complained of symptoms and was of normal intelligence and development. Her Hb level is 13.2g; PCV is 40%; MCHC 33%; G6PD activity 40; Hb F 0.6%. Her diaphorase level is 0 (Control over 400). She has since married and is now pregnant. The diaphorase of six healthy siblings of the above two cases (6 and 7) varied from 95 to 304.

The father's diaphorase level was 115 while the mother's was 90. (Control over 400).

Discussion

These are the first families of diaphorase deficiency methaemoglobinaemia to be recorded from the Maltese Islands. Though most of the cases so far described in the world literature have been in Europeans or in persons of European stock, interesting geographical concentrations of the disease have been described. Thus Scott and Hoskins (1958) found fifteen affected persons arising from 9 families of Alaskan Eskimos and Indians in four areas of Alaska. Four of these nine families were interrelated. A relatively high gene frequency has also been found among the Navajo Indians (Balsano *et al.*, 1964). The condition is of world wide distribution as cases have been recorded among North Africans (Rousell *et al.*, 1963), Chinese (Chang and Wu, 1954), Hindus (Raj *et al.*, 1959) and Puerto Ricans (Jaffe *et al.*, 1966). The incidence of this recessively inherited disease therefore is relatively high in the Maltese Islands whose total population is only one third of a million inhabitants.

The degree of methaemoglobinaemia has been noted to fluctuate from season to season and with age. Thus Scott and Hoskins (1958) found that methaemoglobin levels in their Alaskan patients were less in September than in December fifteen months later. They postulated an environmental factor such as ascorbic acid. The same workers also noted a tendency for the methaemoglobin levels to fail with age. They recorded a patient who had a level of 22 per cent methaemoglobin when eight years old, and 4.8 per cent when re-examined eight years later. It is interesting to note in this connection that Case 6 was described by her parents to have had obvious cyanosis in early childhood and that this had slowly disappeared with the years only to reappear when she became pregnant. The methaemoglobinaemia also

became more aggravated with pregnancy in Case 4. The cyanosis of methaemoglobinaemia in pregnancy has been mistaken as being due to cardiac disease as has been pointed out by Vassallo and Cauchi, (1970). This aggravation by pregnancy has also been noted by other workers, and pregancy may be the factor that leads to the diagnosis of methaemoglobinaemia. (Pepper, Weinstein and Heller, 1961).

None of the patients had been taking any drugs. The recessively inherited form of congenital methaemoglobinaemia appears to have been first described by Hitzenberger (1932) who described a mentally defective dwarf with a strong family history. Sievers and Ryan (1945) suggested that the defect lies in the reduction system of methaemoglobin. Gibson (1948) showed that the enzyme diaphorase was missing in methaemoglobinaemic cells as methylene blue was extremely effective in reducing methaemoglobin. Diaphorase (diphosphopyridine reductase DPNH, NADPH, coenzyme factor 1) is an intermediate carrier which catalyses the reduction of methaemoglobin by reduced diphosphoryridine nucleotide (DPNH). Another far less important pathway for the reduction of methaemoglobin is mediated by Diaphorase 11 (reduced triphospopyridine nucleotide, TPNH, NATPH). (Huennekers *et al.*, 1957). Other unimportant systems known for the reduction of methaemoglobin in normal cells are ascorbic acid (Lian, Frumusan, and Sassier, 1939) and by means of reduced gluathione (Scott, Duncan, Ekstrand, 1965). Lately another enzyme variant in a case of congenital methaemoglobinaemia has been demonstrated (West *et al.*, 1967).

Treatment of hereditary methaemoglobinaemia secondary to diaphorase deficiency is not necessary except in unusual circumstances. Both ascorbic acid (Lian, Frumusan and Sassier, 1939) and methylene blue (JJaffe and Neuman, 1964) are both very efficacious and act by direct chemical reduction of methaemoglobin. Ascorbic acid was used intravenously in our Case 2 during his terminal illness as it was necessary for the oxygen transport system of haemoglobin to be utilised to the fullest extent and for the dead load of methaemoglobin to be minimised.

The discovery of these seven cases clinically would suggest that the relative gene frequency for this recessive type of congenital methaemoglobinaemia is high in the Maltese Islands and that a future systematic survey for diaphorase deficiency among a suitable section of the population such as school children may reveal many more cases.

Acknowledgements

We wish to acknowledge the kindness of the Editor of "The Journal of Obstetrics and Gynaecology of the British Commonwealth" for permission to quote Case 4 (Family B) and Case 6 (Family D).

We wish to thank the personal doctors of the families concerned, for their cooperation.

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THE INVESTIGATION OF AUTOIMMUNE DISORDERS

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Introduction

During the last few years our knowledge of autoimmune disease has increased considerably, and the techniques for detecting such disease have been improved and made simpler. The laboratory tests to detect humoral antibodies in patients suffering from an autoimmune disorder have become routine in a number of hospitals and the use of techniques, and, in particular immunofluorescence techniques, have assumed greater importance.

The purpose of the present communication is to outline some of the available immunopathological techniques and to illustrate how they are applied in the day to day investigation of patients in an acute general hospital.

Immunopathological Techniques

A) *Immunofluorescent methods*

The indirect immunofluorescence technique — also called the "sandwich" method — is used in most cases (Nairn 1969). Normal tissue is snap-frozen in a liquid nitrogen-isopentane mixture (temperature $-180°C$) and stored for future use at $-70°C$. When required, frozen sections are cut and the patient's serum layered on top of the section. *(Fig. 1)*. Antibodies present in the serum will combine with antigenic sites in the tissue section. Excess serum is then washed off, and a fluorescene-conjugated rabbit anti-human globulin is applied to the section

— this last layer will attach to any globulin remaining on the section, thereby localising any antigen-antibody reaction.

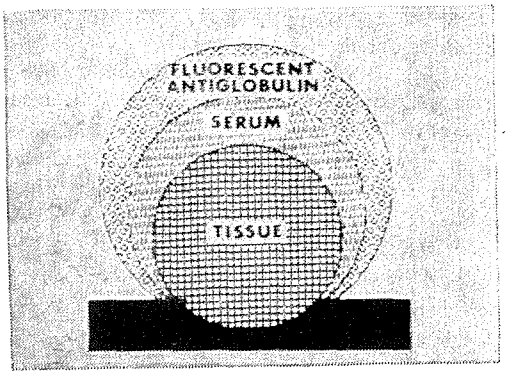

Fig. 1

Using this method a number of tests have been devised to detect antibodies in human sera. Antinuclear antibodies *(Fig. 2)* are best detected using rat liver sections.

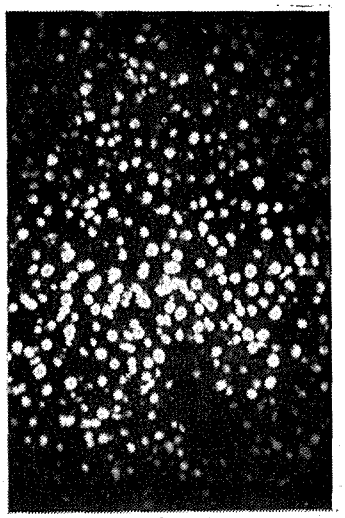

Fig. 2

Such antibodies are present in about 100% of patients suffering from lupus erythematosus. Antibodies to gastric parietal cells can likewise be demonstrated in the sera of 90% of patients suffering from pernicious anaemia. (McKay, 1969) *(Fig. 3)*. In autoimmune disorders affecting the thyroid gland, two distinct antibodies may be detected by immunofluorescence. Firstly a cytoplasmic antibody reacting with the cytoplasm of cells lining the vesicles *(Fig. 4)*, and secondly, an antibody reacting with thyroglobulin *(Fig. 5)*. Antithyroglobulin antibodies are present in 90% of patients with Hashimoto's disease and

Fig. 3

Fig. 4

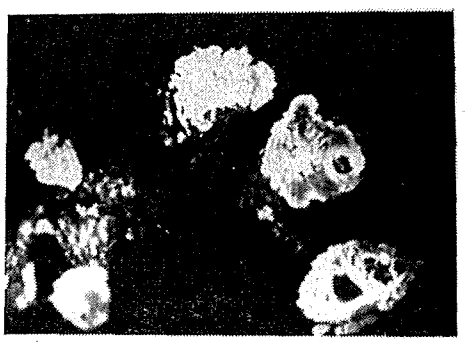

Fig. 5

anticytoplasmic antibodies are present in about 70% of patients with thyrotoxicosis.

Other immunofluorescence tests that yield useful information are:

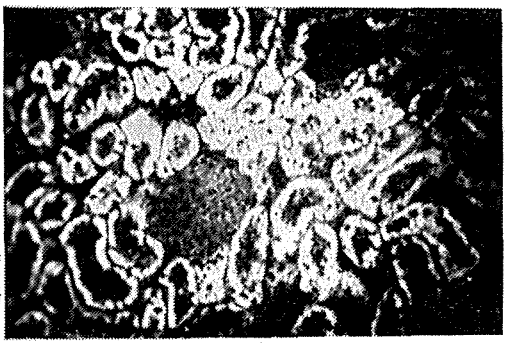

Fig. 6

a) Antimitochondrial antibodies *(Fig. 6)*. These antibodies, best detected in kidney tubule cells are present in about 79-94% of patients with primary biliary cirrhosis, and since such antibodies are not present in patients with extrahepatic jaundice, their presence is useful in the differential diagnosis of these two condition. (Brit. Med. J. 1970, Doniach 1968 .

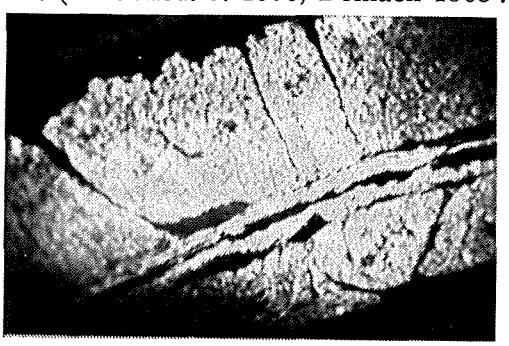

Fig. 7

b) Anti smooth muscle antibodies *(Fig. 7)*. These are present in cases of lupoid hepatitis.

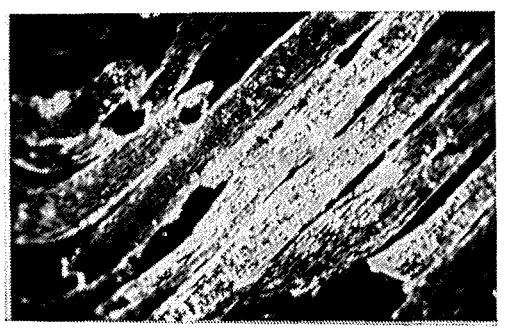

Fig. 8

c) Anti striated muscle antibodies *(Fig. 8)* are present in cases of myasthenia gravis, about 30% of which show the typical band fluorescence.

d) Anti adrenal cortex antibodies are present in about 50% of patients with Addison's disease.

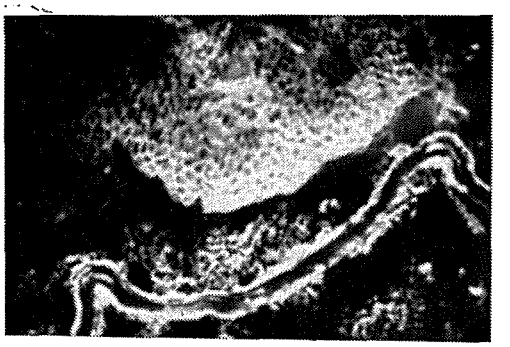

Fig. 9

e) In skin disorders, antibodies against the intercellular area and cell membranes of squamous epithelium are present in pemphigus vulgaris *(Fig. 9)*, while anti-basement membrane zone antibodies are present in Bullous pemphigoid *(Fig. 10)*. So characteristic are these changes that the presence of such antibodies is virtually diagnostic. (Muller and Sutherland, 1970).

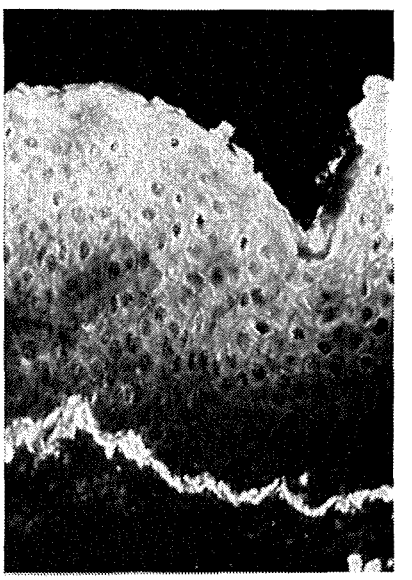

Fig. 10

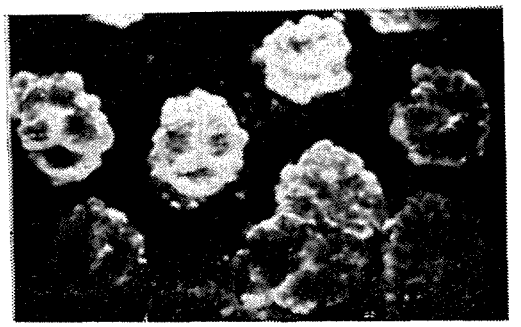

Fig. 11

f) In ulcerative colitis, anticolon mucus antibodies can be detected *(Fig. 11* . (McGiven *et al.,* 1967).

g) Using specific antisera to immunoglobin IgG, IgM, IgA as well as antifibrin, anti complement etc., direct visualisation of the exact nature of antigen antibody complex can be achieved. (This is an example of the direct immunofluorescent technique, as opposed to the above test where the indirect test is used).

B) Tanned Red Cell Haemagglutination Technique

Tanned sheep red cells have the power of combining with a number of antigens (Herbert, 1967). Thyroglobulin is such an antigen that can be readily attached to sheep red cells to produce a very useful reagent for the detection of antithyroglobulin antibodies. Briefly, thyroglobulin-coated cells (supplied by "Wellcome") are added to a series of tubes containing se-

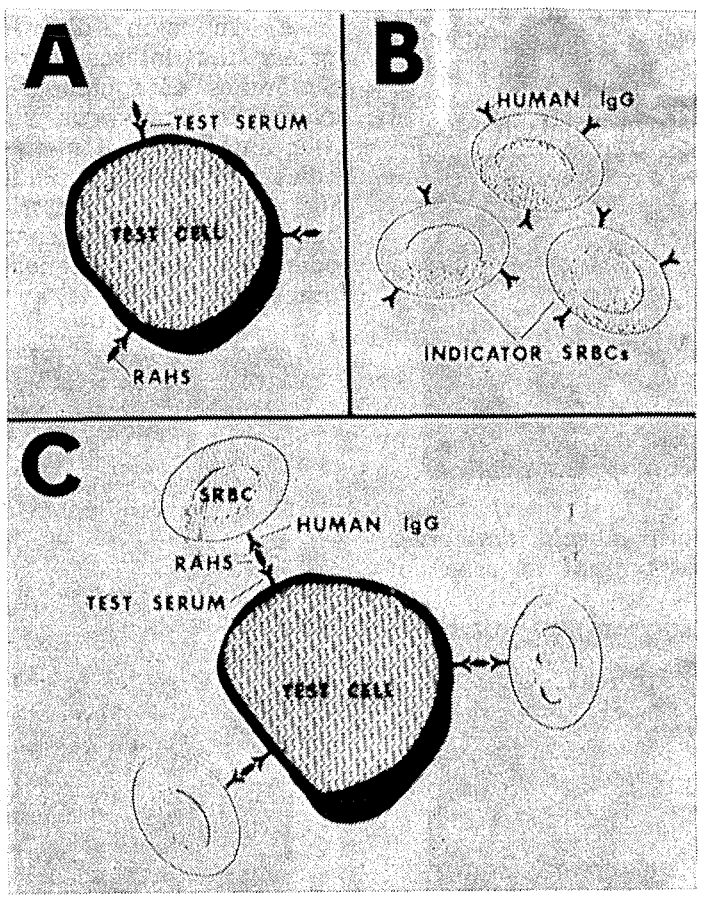

Fig. 12

rial dilutions of the patient's serum. Agglutination of the red cells occurs in those tubes containing sufficient antibody. In Hashimoto's disease, this test is positive in 90% of cases (McKay, 1969).

C) Latex Agglutination

In rheumatoid arthritis, the latex agglutination test is used to detect rheumatoid factor. Latex particles coated with human γ globulin are supplied in kit form (Hyland). When one drop of test serum (diluted 1/20) is added to 1 drop of latex-globulin reagent, macroscopic clumping occurs.

Other Tests Not Used Routinely

A) Mixed Antiglobulin Test (Coombs and Gell, 1968)

This is a very sensitive test for detecting very small amounts of circulating antibodies to cellular constituents, such as peripheral blood lymphocytes, tumour cells, etc. In principle, *(Fig. 12)*, lymphocytes or other cells to be tested are washed free of serum and the test serum is then added. After a suitable interval, the cells are washed again and antihuman serum (e.g. rabbit antihuman globulin) is added so that the cells are coated with a layer of human serum, and then with a second layer of rabbit anti-human globulin *(Fig. 12A)*. As an indicator system, sheep red cells coated with human globulin are used *(Fig. 12B)*. When mixed together, typical rosettes are formed consisting of a central lymphocyte surrounded by sheep red cells *(Fig. 12C, Fig. 13)*. This technique can be used to demonstrate specific antibodies to cell membranes such as antibodies to tumour cells (Mori and Coombs, 1969).

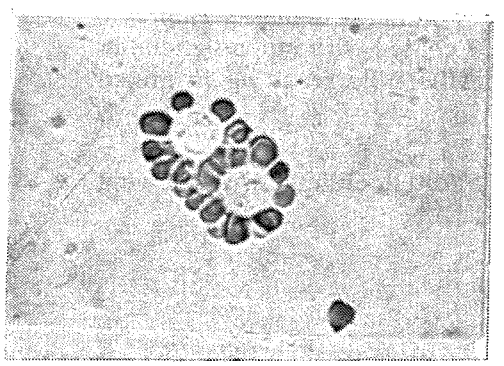

Fig. 13

B) Membrane Immunofluorescence

In routine immunofluorescence tests, the tissue is frozen — a process which kills cells — and then serum is layered on, so that it comes in contact with the intracellular constituents, e.g. cytoplasm, nuclei etc. The technique of membrane immunofluorescence enables the detection of antigens present on the membrane of cells, and in this context it is well to remember that the cell membrane may well be a very important antigenic constituent in a number of immunological situations.

Theoretically, the technique of membrane immunofluorescence is quite simple. The cell suspension to be tested (e.g. tumour cells) is first washed, and then the test serum is added. After half an hour, the cells are again washed and fluorescene-conjugated antihuman globulin added. A drop of cells is then examined by fluorescent microscopy. When the reaction is positive, the cell surface shows a ring of bright fluorescence.

The main value of this technique is to localise antigens situated on the cell surface, such as tumour specific transplantation antigens, HL-A antigens, etc.

The Routine Investigation of Patients Suffering from Autoimmune Disease

The rest of this communication will deal with the results obtained from tests performed on 1000 consecutive patients suffering from a number of unrelated disorders. It is to be emphasised that these results do not in any way represent a survey of the incidence of the various diseases. Rather it is hoped that these results will illustrate a number of facets common to autoimmune disease in general.

As seen in *Table 1*, out of 1000 patients tested, 481 had one or more positive tests. The very high incidence illustrates the selection of cases referred for

LEGENDS TO FIGURES:

Fig. 1. Diagrammatic representation of the indirect immunofluorescence test. (See text).

Fig. 2. Anti nuclear antibodies. Liver sections treated with anti ANF sera show bright staining of cell nuclei.

Fig. 3. Anti gastric parietal cell antibodies. Sections of stomach fundus to show positive parietal cell staining.

Fig. 4. Anti thyroid cytoplastic antibodies to show staining of cytoplasm in human thyroid.

Fig. 5. Anti thyroglobulin. Typical flocculent staining of colloid inside thyroid vesicles.

Fig. 6. Anti mithochondrial antibodies. Kidney sections showing cells lining the tubules staining positively. The glomeruli are negative.

Fig. 7. Anti smooth muscle antibodies.

Fig. 8. Anti striated muscle antibodies.

Fig. 9. Anti bodies to intercellular area from a case of pemphigus vulgaris (courtesy of Dr. H. K. Muller).

Fig. 10. Anti basement membrane zone staining in Bullous pemphigoid (courtesy of Dr. H. K. Muller).

Fig. 11. Anti colon mucus antibodies in ulcerative colitis.

Fig. 12. Principle of the mixed antiglobulin test:
A: Test cell coated with test serum and anti human serum.
B: Indicator Sheep Red Blood Cells coated with human globulin.
C: Mixing of test cells with indicator cells resulting in mixed agglutination.

Fig. 13. Rosette formation in the Mixed Antiglobulin Test, showing lymphocytes surrounded by red cells.

TABLE 1
Incidence and sex ratio of patients having one or more positive immunological tests

		M : F Ratio
Number of patients tested	1000	1 : 1.5
Number of patients with positive tests	481	1 : 1.9

immunological studies. It is to be noted that the sex ratio of patients having a positive immunological test is heavily loaded towards females in the ratio of 1 : 1.9 (compared to 1 : 1.5 for the patients in general).

TABLE 2
Incidence of individual positive results

Test	Number positive
Anti nuclear factor (ANF)	82
Anti gastric parietal cell (AGPC)	260
Anti thyroid cytoplasm (Cyto)	130
Anti thyroid colloid (Coll)	32
Anti mitochondrial (Mito)	13
Anti smooth muscle (S M)	30
Rheumatoid Factor (R.A.)	92
Tanned Red cell Agglutination (TRC)	78

Table 2 shows the incidence of the individual positive tests. Antigastric parietal cell antibodies were the commonest ones encountered (26%). Antithyroid tests (including anti-cytoplasmic, colloid, and tanned red cell tests) were positive in 3.2–13.0% of the patients, depending on the test used. Antinuclear factor was evident in 8.2% of patients.

TABLE 3
Patients having "single" or "multi" system involvement *

Number of patients having one positive test	298
Number of patients having two positive tests	136
Number of patients having three positive tests	47

(* Anti thyroid cytoplasmic and anti thyroid colloid antibody and tanned red cell agglutinaiton represent one single system involvement, and hence were counted as one test for the purpose of this table.)

In many cases there was more than one antibody present in the serum. *Table 3* shows that 136 patients had two positive tests. (For this purpose, the three different antithyroid tests, viz, anti cytoplasmic, anti colloid and tanned red cell agglutination, were considered as one test). 47 patients had antibodies reacting with three different systems, e.g. antigastric, anti thyroid as well as anti nuclear. This relationship is further analysed in *Table 4* which illustrates the frequency of association of antibodies in autoimmune disorders. For example anti parietal cell antibody is found associated with anti thyroid cytoplasmic antibody in 51 patients, and with RA test in 33 patients. Similarly, antithyroid cytoplasmic antibody is found in 15 patients having anti nuclear factor, in 24 patients having anti colloid, in 51 patients having a positive TRC, as well as in 15 patients having a positive RA.

TABLE 4
The frequenecy of association of positive tests

	ANF	AGPC	CYTO	Coll.	Mito	S.m.	RA	TRC
ANF	—	17	15	2	—	2	19	12
AGPC	17	—	51	13	9	7	33	34
Cyto	15	51	—	24	4	3	15	51
Coll	2	13	24	—	1	1	5	23
RA	19	33	15	5	3	1	—	10
TRC	12	34	51	23	2	4	10	—

To be noted also the high incidence of anti gastric parietal cell positive sera in RA positive patients. RA tests were not done routinely on all patients, but there was no reason to suspect that AGPC positive patients were selected for RA tests. Tanned red cell tests were done only on those patients with a positive anti cytoplasmic or anti colloid antibody. This explains the positive correlation of immunofluorescent tests for thyroid disease and a positive TRC: Out of 78 patients with positive TRC test, 51 were associated

with a positive anti thyroid cytoplasmic antibody, and 23 with anti thyroid colloid antibody. The association of positive TRC and anti AGPC however represents the association of autoimmune disease affecting both thyroid and gastric cells.

Although the data presented above are selected and not meant to indicate the true incidence of autoimmune disease, nevertheless several important conclusions can be drawn from this study:

1) The importance of performing immunological tests on patients in a general hospital population.

2) The greater incidence of autoimmune disease in females.

3) The importance of testing all patients with a battery of tests and not just with a single test. In many instances it can be shown that the patient serum was negative for a suspected lesion, e.g. ANF, but positive for AGPC or antithyroid antibodies.

4) It has further been shown that in certain instances which are not uncommon, a "multisystem" autoimmune disorder is present associated with a whole host of abnormal antibodies.

5) Finally, in drawing any conclusions from immunological tests of this nature it is important to keep in mind the tendency for antibodies to appear with advancing age (Whittingham *et al.*, 1969). Apart from the fascinating correlation between the process of ageing and autoimmune disease which this observation entails, it is essential to keep in mind the fact that the presence of antibody is not necessarily causing the disease, but may be a secondary accompaniment of tissue breakdown and destruction. It has been shown, for example, that destruction of peripheral blood cells by irradiation is followed by antileucocyte antibodies in the serum (Suzuki, 1969), and that the level of antibodies to Burkitt Lymphoma cells is greater after chemotherapy, which presumably involves massive destruction of tissue and cells (Yata *et al.*, 1970). It is conceivable that some similar or related process is occurring in the aged population.

In all cases, however, a careful assessment of the immunological status of patients suffering from a variety of (usually chronic) disorders, using both humoral antibody techniques described above, as well as techniques that measure the cellular immunological potential, are essential in the proper evaluation of the immunological status of patients.

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CONTRAST RADIOLOGY OF THE SMALL BOWEL

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Summary

The various methods for small bowel examination are discussed and relevant details of techniques given. Their respective advantages and limitations are given.

It is concluded that the small bowel enema is the most accurate method for small bowel study.

The radiological examination of the small bowel should begin with plain radiography, erect and supine, of the abdomen. The usefulness of the plain films of the abdomen in the diagnosis of intestinal obstruction or perforation is well known. What is not so well established is the most suitable and most informative method for barium small bowel study.

Barium can be introduced into the small bowel antegradely, retrogradely or through a duodenal tube. The purpose of this paper is to give details of techniques and to compare the advantages and limitations of the various methods and thereby conclude on which should be the method of choice.

A. Antegrade method.

This is really a continuation of the radiological study of the upper gastro intestinal tract. It usually consists of a series of radiographs of the abdomen at certain intervals after the ingestion of the barium suspension. The investigation of the small bowel by such routine "barium meal and follow-through" has the disadvantage that the sphincteric action of the pylorus usually prevents a continuous filling of the small bowel. Also a lesion can easily be missed on account of the anatomy of the intestine, consisting of short loops forming a sinuous course and the diseased area can easily be overlapped and consequently obscured. Besides this, this method is time-consuming. Some people recommended mixing barium with ice-cold normal saline solution instead of plain water — this is said to hasten the transport through the small intestine and thus shorten the time taken by the examination.

Recent work has shown that such "follow-through" methods could be improved if a continuous flow of barium through the pylorus could be obtained. Neostigmine (adult dose 0.5 mgms. intravenously) has proved of some help and the small bowel is more rapidly and uniformly outlined (Margulis and Mandelstam, 1961). Neostigmine is said to increase the activity of the involuntary muscles and hence gastric evacuation is hastened. More recent studies have shown that Maxolon might be more efficient in this respect. It dilates the pylorus and duodenal cap and improves the peristalsis in the stomach. Hence gastric emptying is improved and the transit of the barium through the small intestine is hastened.

Maxolon is well absorbed by oral, intramuscular and intravenous routes and is available as tablets, syrup and ampoules for injection. We found the syrup and tablets adequate and doses of four teaspoonfuls (20 mgm.) of syrup or two tablets (10 mgm. each) thirty minutes before the barium meal hastened the transit of barium through the small bowel.

B. Retrograde method

This examination was first described by Greenspon and Lentino in 1960. It con-

sists of reflux filling of the small bowel from a barium enema examination, giving about 1500 ml. of barium suspension through a wide bore tubing followed by about 2000 ml. of saline.

C. Small bowel enema

This procedure aims at excluding the pyloric sphincter and giving a continuous flow of the barium suspension directly into the distal duodenum through a tube (Scott Harden 1960) and thus rapidly filling the small bowel. The "solution" is gradually propelled through successive loops of the small bowel under television screening; it not only fills the small bowel systematically but it also distends the intestine. By this means the whole length of the small bowel can be surveyed in about 15 minutes.

Technique

Preparation of patient

The patient is prepared as for a barium meal. The whole procedure is explained to the patient to get full co-operation.

A lignocaine lozenge is sucked beforehand, to help swallowing the tube. *Tube:* The tube I have been using is the Portex Scott-Harden duodenal intubation tube (Cat. No. G417 Mk. 2) which consists of an outer (gastric) sheath and an inner (duodenal) tube. At the end of the duodenal tube about 6 c.m. length of a Ryle's tube is fitted. This intubation tube is manufactured from polythene tubing and is easily seen on fluoroscopy. The patient, sitting up, swallows the tube; he is then screened in an erect position and the tube is advanced along the greater curvature of the stomach until the end of the Ryle's tube is pointing towards the pylorus. The patient is then put supine and the duodenal tube is gently pushed to pass through the pylorus into the duodenum until the end lies near the duodeno-jejunal flexure.

Contrast Medium

The solution used is equal parts of 50% Micropaque in water, normal saline and 1% prepacol. About 1,500 m.l. of the mixture is used together with some air which increases the double contrast effect.

The prepacol solution should be freshly prepared from very fine prepacol granules dissolved in cold water (10°-12° C) and the solution should be stored in a refrigerator until required, otherwise it tends to throw a precipitate. Prepacol which is a bulk producing, water retaininng gel, acts as a hastener; it has recently been withdrawn from the market.

In this hospital prepacol is now replaced by a sodium carboxymethyl-cellulose solution. We find the latter just as efficient a hastener as the former. The flow of the mixture must be steadily maintained until the caecum is filled. This is usually done in 15-20 minutes. Besides this solution, we have also been injecting air — 100 ml. of air after every 200 ml. of the solution. This enhances the double contrast effect.

The only side-effects noted were:

a) Nausea if there was reflux of the "solution" in the stomach. This could usually be prevented by positioning the tip of the catheter in the distal part of the duodenum.

b) Feeling of distension towards the end of the examination. This seemed to be related to the amount of the "solution" given. We found 1500 ml. of the solution to be adequate.

The object of this procedure is to obtain an unobscured outline, in successive segments, of the whole length of the small bowel under direct television screening.

Discussion

The radiological examination of the small bowel is considered inadequate in most hospitals. This is probebly due to the fact that most radiologists rely on haphazard barium-meal follow-through radiographs to exclude small bowel pathology, whereas in the case of the upper alimentary tract and large bowel the examination is carried out under screening.

In the routine "follow-through" examination, the small bowel filling is gov-

erned by an unpredictable rate of barium passage through the pylorus. This intermitent and irregular flow of contrast through the pylorus can be controlled by iatrogenically dilating the pylorus, increasing the gastro-intestinal motility of the stomach and also relieving any spasms which might be present. In my experience Maxolon is more efficient than neostigmine in accelerating the transit through the gastro-intestinal tract.

In both of these methods, however, there is no chance of a systematic examination of the whole length of the small bowel and a lesion can easily be missed. Also there is usually incomplete filling due to peristaltic waves. This lack of complete filling and inability to test the elasticity of the bowel wall are the most severe limitations of the follow-through method. Consequently such an examination should be considered as a "general survey" of the small bowel and not suitable to exclude a small and localised small bowel lesion. Within the last two years we have seen three cases in this hospital where the small bowel was considered to be normal by a "follow-through" examination and later were shown to have Crohn's disease by a small bowel enema *(Fig. 1)*.

The reflux examination of the small bowel has never become popular in England. Although my experience with this method is limited, a proportion of the pa-

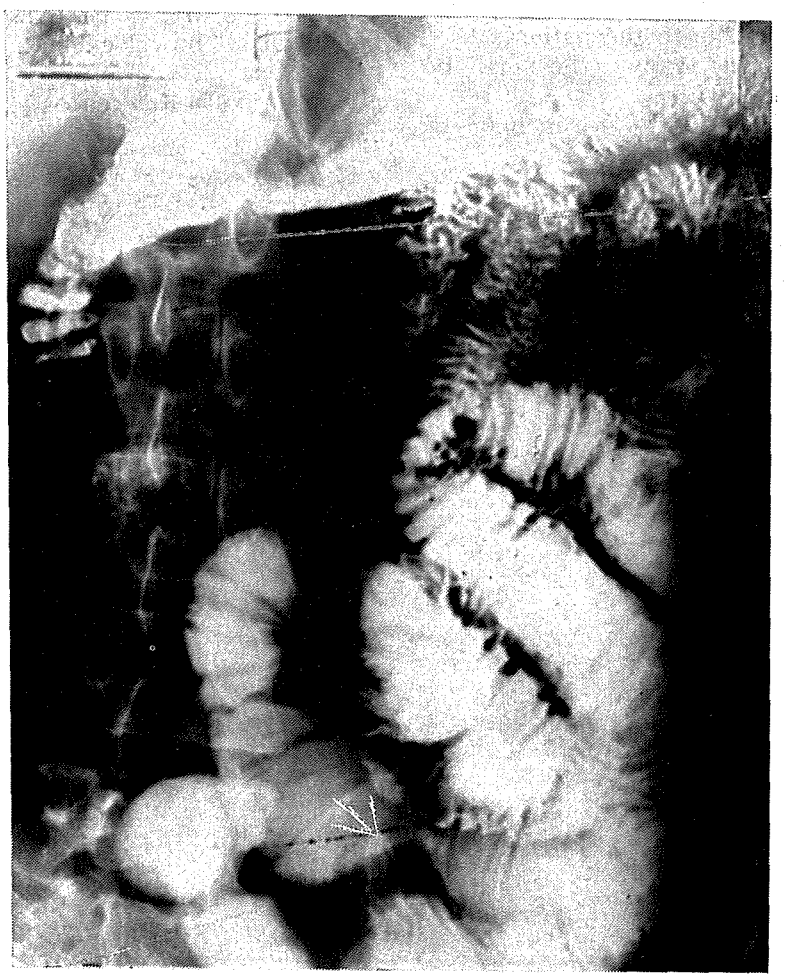

Fig. 1. Small bowel enema.
Arrow points to a stenotic lesion due to Crohn's disease.

tients cannot be examined in this fashion either because the patient cannot retain the enema or else because of failure of the barium to reflux through the ileocaecal valve. This examination is not only uncomfortable but painful. Besides, it is also possible for a small lesion in the terminal ileum to be obscured by a barium-filled, overlapping caecum and occasionally a large redundant colon will complicate the interpretation of films.

The small bowel enema gives an antegrade study where the pyloric sphincteric action is eliminated. The transit of contrast along the small bowel depends on the continuous flow of barium solution and the "hastener". The procedure in the hands of an experienced examiner is quick, systematic and hence more accurate; it is fairly comfortable to the patient.

Disease in and around the small bowel can interfere with:

a) Its distensibility — it may become irregular or eccentric.

b) The mucosal folds — they may become thickened or absent.

c) The lumen — may be distended or contracted.

d) The bowel wall — may become thickened.

Small barium enema is the only examination which can take in consideration all these aspect.

Conclusions

1. "The follow-through" small bowel examination can be misleading although its efficiency is improved by Maxolon. However, it should be considered only as a general survey of the small bowel.

2. The reflux examination should not replace the antegrade approach but is usualy carried out after inconclusive antegrade studies. (Miller, 1969). Perhaps it has got some part to play in the study of the terminal segment of the ileum, especially as the highest incidence of disease in the small bowel is located here.

3. The small bowel examination of choice, especially if a small lesion or multiple lesions are to be examined, should be the small bowel enema.

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DE LANGE SYNDROME — A CASE REPORT

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We ought not to set them aside with idle thoughts or idle words about "curiosities" or "chances". Not one of them is without meaning; not one that might not become the beginning of excellent knowledge, if only we could answer the question — why is it rare? or being rare, why did it in this instance happen? — James Paget, 1882 *Lancet,* 2:1017.

In 1933 the Dutch paediatrician Cornelia de Lange described a new syndrome of mental retardation occurring in children with a characteristic facies (de Lange, 1933). The syndrome is rare, and just over 200 cases have been mentioned in the literature (Abraham and Russell, 1968). I report here a patient with the de Lange syndrome who also has a rare type of cyanotic congenital heart disease.

Case Report

The 5-year-old patient is the illegitimate daughter of a secundiparous epileptic and mentally retarded Maltese mother. She was born at 38 weeks after a normal pregnancy and breech extraction. The birth weight was 2580 grams (5 lbs 6 oz). There were no respiratory difficulties at birth.

At 6 weeks of age prior to her discharge from hospital weighing 3300 grams (6 lbs 14 oz), the child was found to have a loud systolic cardiac murmur. Subsequently, she failed to thrive and suffered from repeated chest infections. It soon became obvious that the child was severely mentally retarded and because of the unsatisfactory home background she was for a time placed in an institution.

She is now 5 years old, shows considerable delay in both her mental and physical development and takes only a limited interest in her surroundings. Her speech maturation is especially defective, and she cannot produce an intelligible sound. She can barely sit up unsupported and cannot eat any solids. She rarely smiles, is easily upset when handled and frequently indulges in head banging, body rocking and hair pulling.

On examination, she is an ugly-looking child with marked central cyanosis and orthopnea and shows the typical de Lange syndrome facies *(Fig. 1)*. Her weight is 8.7 Kg. (19 lbs 1 2oz), her length 82.5 cms (32.5 inches) and the chest circumference: 53.3 cms (21 inches). All these measurements lie well below the 3rd percentiles. The skin shows hypertrichosis and cutis marmorata.

Facies: She is microcephalic—head circumference: 45.7 cms (18 inches)) with a flattened skull (brachycephaly). The hair is lustreless and the occipital and frontal hair-lines are low. The bushy eyebrows meet in the midline (synophyrs), the eyelashes are long and there are bilateral medial epicanthic folds. The bridge of the nose is depressed and the nostrils anteverted. The ears are normally formed but are low-set. The chin is small (micrognathia). The large mouth shows distinctive features. There is an increase in the distance between the nostrils and the upper lip, which has only a small philtrum in the midline. The lower lip is rather prominent and the angles of the mouth curve downwards. There is a high-arched palate and dentition is faulty.

Limbs: Changes in the upper limbs

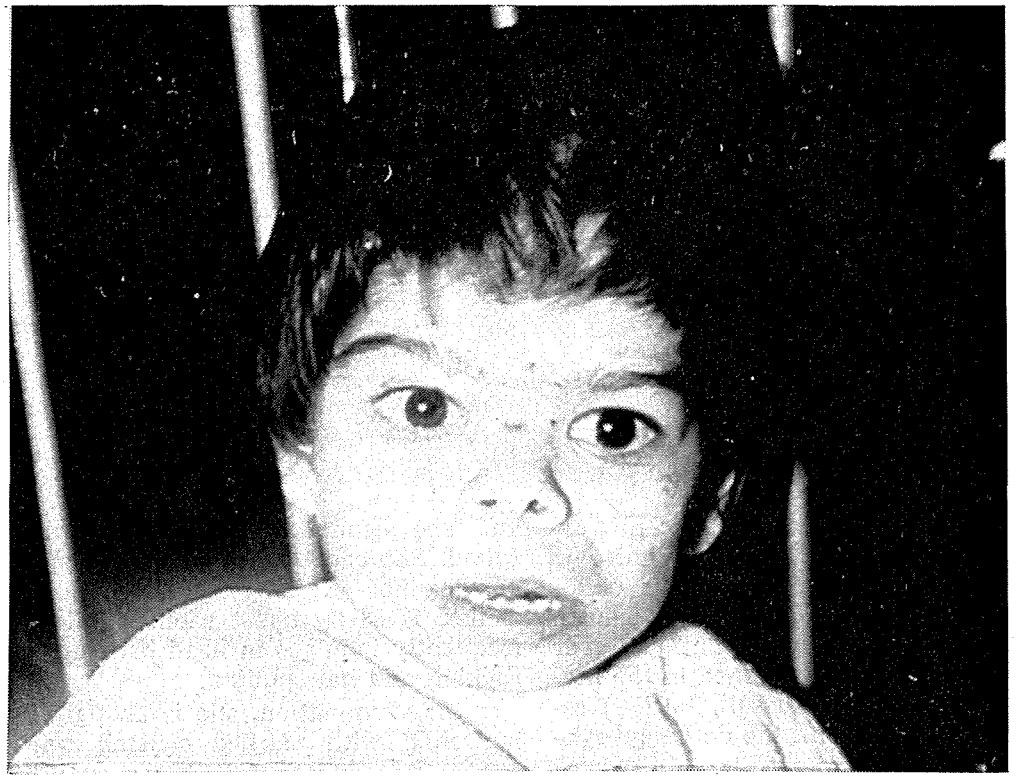

Figure 1

include limited flexion of both elbows, simple palmar creases, slightly incurved little fingers (clinodactyly) and gross clubbing. The thumbs are proximally placed and broad. The legs are thin, the right shorter than the left. There is bilateral genu recurvatum, that on the right being fixed due to contracture of the vastus intermedius. The feet show toe clubbing, minimal overlap of the 4th over the 5th toes and long big toes. The heels are prominent.

Chest and Abdomen: There is dorsal kyphoscoliosis with a slight lateral curve, convex to the left. The chest is barrel-shaped with a marked left chest bulge and a short sternum. The apex beat is in the 4th left intercostal space on the anterior axillary line. There is no right ventricular heave. A grade 3/6 long ejection murmur is heard best at the upper left sternal border. The second sound is single and not accentuated. The lungs are clear to auscultation. The percussion note is tympanitic in the right hypochondrium and the liver edge is palpable on the left. The spleen and kidneys are not palpable.

Investigations carried out are as follows: Hb. 15.7Gm%; P.C.V. 60%; W.B.Cs 7,600/cu.mm Neutrophils: 36%; Lymphocytes: 44%; Monocytes: 17%; Eosinophils: 2%. The peripheral smear shows moderate anisocytosis, poikilocytosis and anisochromia. Occasional target cells are present. No stippled erythrocytes, Howell-Jolly bodies, Heinz bodies or nucleated R.B.Cs are seen.

The E.C.G. shows the Wolff-Parkinson-White syndrome. There are also upright P waves in leadsI, aVL and left ventricular chest lead and bi-ventriculra hypertrophy more right then left.

X-Ray Chest and Upper Abdomen *(Fig. 2)* shows gross cardiomegaly with a ball-shaped heart, with the cardiac apex pointing to the left. The lung fields are cligaemic. The liver shadow is present on the left side and the stomach and intes-

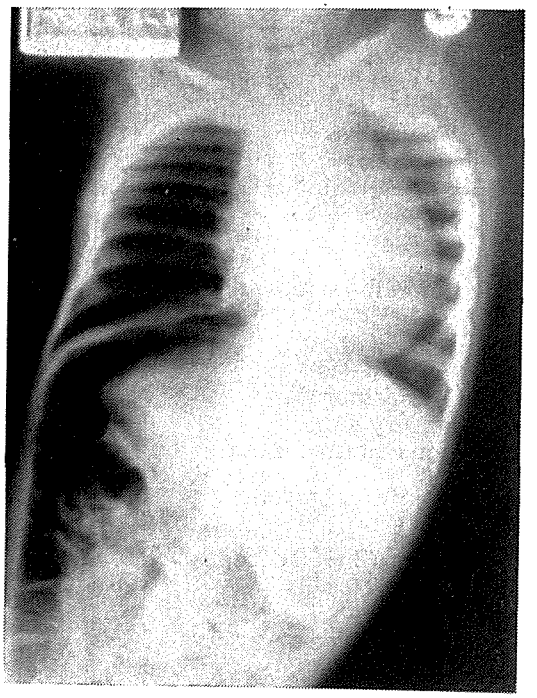

Figure 2

tinal gas shadows are mainly on the right side. No spleen shadow is visible. X-ray hands and forearms shows delayed bone age (corresponding to that of a $2\frac{1}{2}$-year old), rather small but thick 1st metacarpals and small middle phalanges of the fifth fingers. The head of the radius appears normal but the glenoid fossa is rather shallow on both sides.

Comments

This patient shows most of the classical morphological characteristics of the Cornelia de Lange syndrome. The table compares the clinical features of this case with those of the 9 cases described by Abraham and Russell (1968).

The aetiology is still uncertain and the vast majority of cases are sporadic. Various chromosomal anomalies have been observed in a few of the cases who have had chromosome analysis but the significance of these findings is still doubtful.

Diagnosis of the condition rests chiefly in recognising the combination of severe mental and physical retardation and the peculiar facies. Of the facial features, the two most important are the bushy eyebrows meeting in the mid-line and the curved, thin upper lip with absent philtrum and sometimes with a corresponding notch in the lower lip. Certain X-ray abnormalities are also characteristic, notably the short thick 1st metacarpals and the small, sometimes rudimentary 2nd phalanges of the little fingers. The heads of the radii are also not uncommonly malformed. Bone age is delayed in most cases.

Studies in dermal ridge patterns of the hands (dermatoglyphs) have shown mainly an increased number of radial loops in the finger tips of the middle three fingers and commonly, a loop from the c triradius into the third interdigital space of the palm (Smith 1966).

Congenital heart disease is not uncommon in these patients. With situs inversus of the abdominal viscera, there is usually dextrocardia. Rarely, as in the case here described, situs inversus is associated with a normally-placed heart — a condition known as "situs inversus with laevocardia". Campbell and Forgacs (1953) could only discover 14 cases among 1130 patients with congenital heart disease, an incidence of about 1%.

In the majority, the heart chambers are normally placed but in one-third of cases inversion of the atria is also present. This may or may not be accompanied by corresponding inversion of the ventricles. Irrespective of whether chamber inversion is present or not, multiple and extremely complex cardiac lesions, usually of the cyanotic group, generally accompany this anomaly. These include: 1) abnormal systemic vein connections; 2) anomalies of the great vessels and septal defects; and 3) right- sided aortic arch (Gasul *et al.* 1966).

Two other interesting defects often coexist. Firstly, there is in the majority of cases abnormal lobulation of the lungs, which are symmetrical and have three lobes each. Secondly, congenital absence or agenesis of the spleen (asplenia) is common. This is usually associated with repeated severe chest infections and the presence of numerous Howell-Jolly bodies (nuclear remnants) and Heinz bodies

		Present case			Present case
FACIES			HANDS		
Synophrys	9/9	+	Proximal thumb	8/9	+
Long upper lip	9/9	+	Fifth clinodactyly	8/9	+
Anteverted nostrils	8/9	+	Simian crease/s	9/9	+
Depressed nose bridge	6/9	+	Tapering fingers	4/9	−
Hypertelorism	3/9	−	Finger clubbing	2/9	+
Anti-mongoloid slant	5/9	−			
Epicanthic folds	2/9	+	ARMS		
Eccentric pupils	4/9	−	Limited elbow movements	3/9	+
Micrognathia	7/9	+			
Prominenet symphysis mentis	4/9	−	SKIN		
High arched palate	3/9	+	Hypertrichosis	8/9	+
Long eyelashes	O	+	Cutis marmorata	7/9	+
Low-set ears	O	+	Rough dry skin	4/9	−
			Ginger coloured scalp hair	2/9	−
SKULL					
Microcephaly	9/9	+	FEET		
Brachycephaly	5/9	+	Webbing (2 + 3) toes	8/9	−
X-RAY CHANGES			OTHERS		
			Growling voice	6/9	+
Short thick 1st metacarpal	9/9	+	Heart murmur	4/9	+
			Birth weight < 6 lb.	9/9	+
Small 2nd phalanges 5th fingers	9/9	+	Failure to thrive	9/9	+
			Genu recurvatum	O	+
Malformed dislocated radial heads	2/9	−	Big first toes	0	+

Features of present case compared with those reported by Abraham and Russel (1968).
+ = present; − = not present; O = not mentioned.

(precipitated haemoglobin) in the R.B.Cs of the peripheral smear. Normally, the spleen is able to remove these bodies from within the red cells without destroying them (Crosby 1959). Similar changes to the above occur in the peripheral blood of patients who have undergone splenectomy.

Laevocardia with situs inversus is often missed during physical examination because when the heart is normally on the left, one tends to perform a cursory examination of the abdomen without specifically looking for the relative positions of the liver and of the stomach. It is only recognised retrospectively after X-Ray examination of the chest and upper abdomen.

In the absence of selective angiocardiography in our patient it is not possible to delineate the exact nature of the complex cardiac anomaly.

Acknowledgement

I would like to thank Dr. T. Agius Ferrante for permission to study this case.

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SURVEY OF HAEMOGLOBIN, BLOOD UREA AND PLASMA URIC ACID CONCENTRATIONS AMONG A SAMPLE OF THE MALTESE POPULATION

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Summary

Following a study of 292 male and 41 female blood donors aged 18 to 65 years, it was found that the average haemoblobin concentration is 14.5 mg./100 ml. for males and 12.7 mg./100 ml. for females; Uric Acid values average 4.9 mg./100 ml. among males and 4.3 mg./100 ml. among females; and the mean blood urea values for males and females are 31.8 mg./100 ml. and 30.9 mg./100 ml. respectively.

No correlation was noticed between these values and the ABO Blood group system.

Most of the blood donations came from people whose age ranged from 25 to 49 years.

The primary purpose of this survey was to establish the averages of haemoglobin concentration, blood urea level and Plasma Uric Acid in a sample of the Maltese population.

Collection of Samples

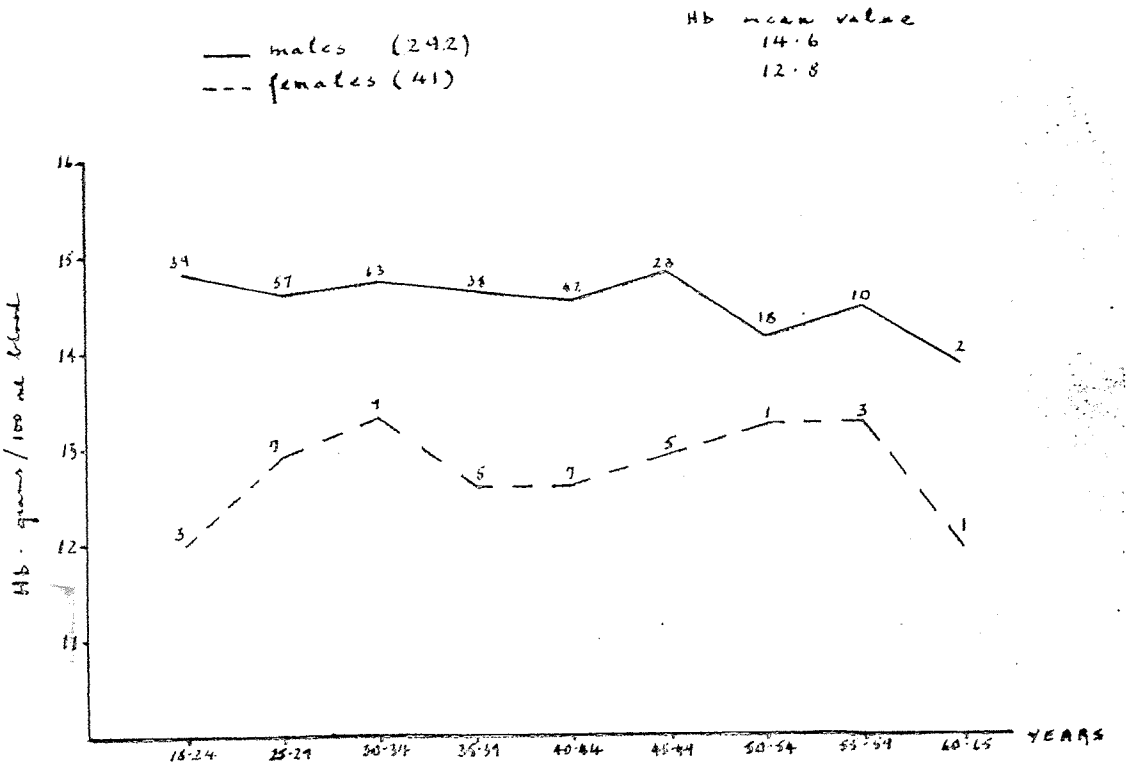
This survey was made on blood donors to the Blood Transfusion Centre at St. Luke's Hospital. Amongst the relatives of patients young men of blood Group O were chosen for preference; this partly explains the low proportion of older subjects and of women, as well as the high percentage of group O donors. Potential donors who were rejected for health reasons were not included.

Blood samples taken at the end of donation with the donor supine, were collected in 5ml. disposable bottles containing Heller and Paul (1934) anticoagulant. Each sample was, in all cases, drawn from the same taking set and the same vein — usually the antecubital vein — used for blood donation.

Haemoglobin estimations were performed within an hour of collection. Cyanmethaemoglobin was determined by diluting 0.02 ml. of blood in 5 ml. of modified Drabkin's reagent. The dilution was compared with a standard Cyanmethaemoglobin solution (obtained from the International Committee for Standardisation in Haematology) using a Unicam S.P. 1300 colorimeter with an Ilford 625 yellow green light filter.

Haemoglobin concentration

There are conflicting results in the various numerous surveys of haemoglobin estimation as affected by age and sex. Hobson and Blackburn (1952) demonstrated a fall in the haemoglobin concentration in both men and women after middle age, while Hawkins *et al.* (1954) have shown a fall in the haemoglobin level of man only after middle age. Cruickshank (1970) showed that while there is a progressive and significant decrease of haemoglobin



Graph 1

concentration in men, on the other hand there is a progressive and significant increase of haemoglobin concentration in women. Our survey — the results of which are shown on Graph 1 — shows that the haemoglobin concentration remains more or less constant until old age in both men and women.

Blood urea levels

In normal adults the blood urea varies according to the protein intake from 12 to 47 mg./100 ml. (Wootton, King and Smith 1957). The actual value for each healthy individual is approximately twice the nitrogen intake in gms./day, e.g. if the nitrogen intake is 11 gms./day, the blood urea averages 22 mg./100 ml. Campbell *et al.* (1968) give a mean value for men of 31.8 mg./100 ml. and for women 28.7 mg./100 ml. These correspond exactly with the values given by Keyser *et al.* (1967).

As Heller and Paul anticoagulant has ammonium oxalate as one of its constituents, urea estimations could not be determined by the urease method; hence measurement of urea level was done by the Diacetyl Method. Estimations were performed the day after blood had been collected.

Table 1 shows that the mean blood urea value is 31.8 mg./100 ml. for males and 30.9 mg./100 ml. for females, figures which compare very well with those of Campbell *et al.*

Table I

Age Groups	18-29	30-39	40-49	50-65	All Ages
Plasma urea values in Males	30.1	31.8	32.5	32.9	31.8
Plasma urea values in Females	29.9	29.6	29.4	35	30.9

Plasma uric acid values

What constitutes the normal range and the mean plasma Uric Acid for both males and female is still to some degree a matter of controversy. Wootton (1951) gives the normal range for plasma Uric Acid as 2 to 7 mg./100 ml. On the other hand C. H. Gray (1967) gives the accepted range as 3 to 5 mg./100 ml. and Milne (1970) gives 2 to 6 mg./100 ml. as the normal range for plasma Uric Acid. Pearce and Aziz (1969) give a mean plasma Uric Acid value of 5.28 mg./100 ml. for males and 4.47 mg./100 ml. for females, Popert and Hewit found a mean of 4.5 mg./100 ml. in 436 males but the levels ranged from 1.9 mg. to 8.1 mg./100 ml.

In our study plasma uric acid estimates were carried out within 24 hours of blood collection. The method followed is that described in King and Wootton 3rd edition 1956. The Standard was prepared from B.D.H. Stock Standard Solution and the results were read on a Unicam Colorimeter using an Ilford 608 light filter. Sodium cyanide — urea reagent and uric acid standard solution were prepared fortnightly.

The results of this survey show, in *Table 2:* a mean plasma uric acid of 4.9 mg./100 ml. for males and 4.3 mg./100 ml. for females, but the levels ranged from 1.6 to 9.4 mg./100 ml. There was no significant rise in level of Uric Acid with advancing age.

Table 2

	18-29	30-39	40-49	50-65	All Ages
Males	4.9	4.8	4.9	5.1	4.9
Females	4.0	4.5	4.2	4.5	4.3

Classification of the blood donors under study according to their ABO and Rhesus Blood groups yielded the following percentages.

47%	O+ve	5.2%	O−ve
39.7%	A+ve	3.3%	A−ve
2.4%	B+ve	1.4%	B−ve
1%	AB+ve	0%	AB−ve

This should not be taken as representative of the distribution of the various blood groups in the Maltese population in view of our preference for donors of blood group O among relatives of patients.

In fact it does not correspond with the percentages issued yearly by the Blood Transfusion Centre at St. Luke's Hospital. This table shows the mean percentages of the past four years.

37.7%	O+ve	3.7%	O-ve
43.9%	A+ve	4.2%	A-ve
6.6%	B+ve	0.7%	B-ve
3.0%	AB+ve	0.2%	AB-ve

The age distribution of the various blood donors shows that the bulk of blood donation comes from age groups 25-29 and 30-34. However, as can be seen from *Table 3:* blood donors come in fairly large numbers from all age groups between 18 to 44 years with a trickle of donors above 45 years.

Table 3

Age & Sex	Distribution of Blood Donors								
Age Groups	18-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-65
Males per cent	13.4	19.5	21.6	13.0	14.3	7.9	6.2	3.4	0.7
Females per cent	7.3	17.1	22.0	12.2	17.1	12.2	2.4	7.3	2.4

Professor Acheson and Dr. Florey have noted in their study an intriguing relationship between the ABO blood group system and the plasma uric acid level, with higher values among persons of blood

Table 4

Relationship between Blood Groups and Uric Acid

Blood Groups	Uric Acid Mean Value
A	4.8
O	4.8
B	4.4
AB	5.5

group A, and lower values among AB individuals. No such relationship was observed in our survey. See *Table 4.*

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THE PALMAR ANHIDROTIC RESPONSE IN CHRONIC SCHIZOPHRENIA

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Summary

1. The palmar anhidrotic response to self-induced stress was investigated in a group of in-patient schizophrenics, a group of out-patient schizophrenics and a group of normal controls. The findings were then related to scores on clinical rating scales measuring the degree of withdrawal and the degree of morbidity both before and during the illness.

2. The control group and the group of outpatients showed normal palmar anhidrotic responses to the stress; the group of in-patients showed a paradoxical increase in the number of active glands immediately after the stress.

3. The basal level of the palmar sweating index was lower in the in-patient group than in the out-patient group and that of the out-patient group was lower than that in the group of normal controls.

4. The findings suggesed that schizophrenic patients characterized by high chronicity, high withdrawal and a poor pre-morbid personality are also subject to some degree of automatic disorganisation.

Autonomic function in schizophrenia has been the subject of sustained interest for many years and the findings from a considerable number of studies have led to the generally accepted notion that schizophrenics show some disturbance of autonomic function. Investigation of basal levels of indices of autonomic function by Gunderson (1953), Howe (1958), Whatmore and Ellis (1958) and Zahn (1964) and reactivity studies by Dmitriev *et al.* (1968) Zahn *et al.* (1968) and others, have confirmed the notion that schizophrenics are

overaroused and hyporeactive, the hyporeactivity probably arising as a result of the high basal arousal level, according to the law of initial values.

One aspect of autonomic function which has been recently highlighted is the palmar anhidrotic response to stress and its modification in schizophrenia (Mackinnon, 1969); the basis of the palmar anhidrotic response (PAR) lies in the fact that activity in the palmar sweat glands is inhibited in normal subjects placed in a situation characterised by psychological stress. Mackinnon *et al.* (1959) showed a decrease in the number of active sweat glands in mountaineers at high altitude and Harrison *et al.* (1962) showed a decrease in sweat gland activity in patients awaiting surgery. Palmar sweat gland activity in these studies was assessed by counts of active glands obtained from plastic casts of a predetermined area of skin from the palmar aspect of the fingers.

In an attempt to isolate the mechanism mediating the PAR, Harrison (1964) and Harrison and Mackinnon (1966) measured the palmar sweating index (PSI) — the number of active sweat glands over an area of skin 4mm square — under various conditions of induced stress and following the administratio nof epinephrine; it was seen that, of the many stresses applied only straight-leg raising produced an anhidrosis similar to that seen in patients awaiting surgery; the PAR could also be brought about by the administration of epinephrine and blocked by the administration of phenoxybenzamine; it was therefore concluded that straight-leg raising constituted a self-induced stress capable of activating both the adrenal cortex and the adrenal medulla.

Mackinnon (1969) has investigated the response of the palmar sweat glands in schizophrenics to self-induced stress and has found that both acute and chronic schizophrenics showed a tendency towards a paradoxical rise in the PSI following the stress.

In an attempt to replicate Mackinnon's findings on the PAR in schizophrenia, a group of chronic schizophrenics was selected and the reaction of the palmar sweat glands to self-induced stress was examined; the findings were then related to clinical state and to the degree of morbidity both before and during the illness, as determined by the appropriate rating scales. Both in-patients and out-patients were tested in order to determine whether the differences in the outcome of the illness were associated with differences in the nature of the sweat gland response.

Methods

Subjects: Forty chronic schizophrenics were tested. The sample was divided into two groups, an in-patient group and an out-patient group; the in-patient group (IPG) consisted of 28 patients of whom 16 were males and 12 were females, the out-patient group consisted of 12 out-patients, of whom 7 were males and 5 were females. A group of ten normal controls, of whom 6 were males and 4 were females, was also tested.

Table 1 gives the mean age, mean chronicity in years and mean drug levels, together with their standard deviations, in the three groups. Mean drug levels were calculated from a survey of all drugs taken by a patient over the three weeks prior to testing; the daily chlorpromazine equivalence was then obtained and the appropriate dosage rating applied (for details see Held *et al.*, 1970).

TABLE 1

	IPG	OPG	NORMALS
Age	43.9	34.6	34.3
S.D.	10.2	6.9	12.2
Chronicity	19.5	9.3	-
S.D.	10.2	5.2	
Drug Level	1.7	1.5	-
S.D.	1.4	0.8	

Measurement of the Palmar Anhidrotic Response

The measurement of the palmar anhidrotic response was carried out by means of a series of estimations of the palmar

sweating index; this was obtained from counts of active sweat glands from plastic casts of the skin over the whorl of the ring finger of the left hand. This method was first described and suggested by Sutarman and Thomson (1952).

Plastic paint was applied to the chosen area of skin and allowed to dry for a period of 20 to 30 seconds; the thin layer of plastic was then detached from the skin by means of a small strip of adhesive tape. The cast thus obtained was then transferred to a labelled microscope slide and examined under the low power of a light microscope. The plastic paint used consisted of a 2/4% (w/v) solution of polyvinyl formal (Formvar) in ethylene dichloride containing 1% butyl phthalate as plasticizer.

The experimental procedure was as follows: subjects were tested singly or in groups of two; a total of six plastic casts were taken in each subject from the same area of skin. The first cast was taken at the beginning of the exeperiment; the second cast was taken immediately before a period of self-induced stress, the third cast was taken immediately after the stress and the final three were taken at subsequent five minute intervals. The self-induced stress consisted of straight-leg raising to the point of maximum endurance; the total time the leg was kept in the air was not considered to be relevant as the main object was to make the subjects drive themselves to the limits of endurance and these limits were expected to vary with age, sex and general physical condition.

The series of impressions thus obtained were examined under the low power of a light microscope and the number of active sweat glands over an area of skin 4mm square was counted; active sweat glands were easily differentiated from inactive glands in that the former give rise to distinct round holes in the cast whereas the latter present a crinkled, closed appearance. The number of active sweat glands over this area was taken as the palmar sweating index and the changes in the palmar sweating index as a result of the self-induced stress were taken as a representation of the palmar anhidrotic response to stress.

The 21 female subjects were tested during the follicular phase of the menstrual cycle; this was done in order to avoid any effects of circulating progesterone on the PSI — it has been shown by Harrison *et al.* (1962) that progesterone tends to lower the level of PSI.

Clinical Rating: In order to obtain a measure of the patient's clinical condition at the time of testing, each subject in the schizophrenic groups was read by the charge nurse or ward sister or, in the case of the out-patients by the experimenter with the cooperation of the families of the patients, on a withdrawal rating scale consisting of items 6, 7, 9 and 10 from the scale devised by Venables (1957) and items 2, 4, 6, 8 from the scale devised by Venables and O'Connor (1959).

In order to obtain an indication of the degree of morbidity both before and during the illness, each patient was rated on items A to F from the Prognostic Rating Scale devised by Phillips (1953); rating was carried out by the experimenter from data obtained from the case notes.

Results

The Palmar Anhidrotic Response: Changes in the PSI were taken as indications of the nature of the PAR; there were differences in the PSI response to stress between the in-patient group and the out-patient group and between the in-patient group and the group of normal controls; there seemed to be no qualitative difference in the PAR between the out-patient group and the control group.

Figure 1 shows the pattern of PSI change before and after the period of self-induced stress; it can be seen that there was a general tendency towards a paradoxical rise in the PSI after stress in the group of in-patients and that the response in the out-patient group was similar to the anhidrotic response shown by the control group.

Figure 2 shows the distribution of the PSI responses in the three groups; it can be seen that in the group of the in-patients

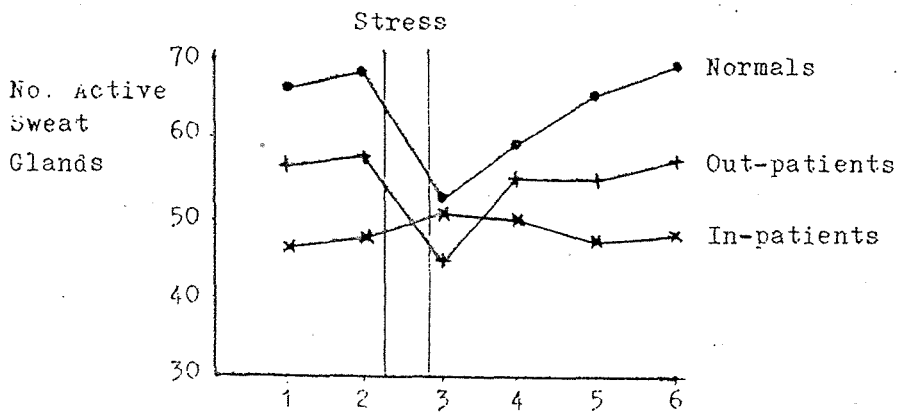

Figure 1 : The pattern of PSI change over time. 1 = Basal, 2 = pre-stress, 3 = post-stress, 4, 5 & 6 = readings taken at 5 min. intervals after stress.

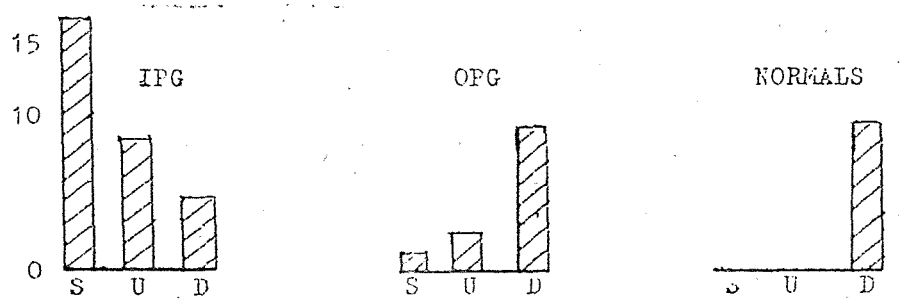

Figure 2 : Distribution of the PAR patterns in the three groups.
S = No change in the PSI after stress
U = Paradoxical rise in the PSI after stress
D = Normal palmar anhidrotic response to stress

there was a paradoxical rise in the PSI after stress in 8 subjects, a fall in 4 subjects and no change in 16 subjects; in the out-patient group there was a paradoxical rise in the PSI in 2 subjects, a fall in 9 subjects and no change in 2 subjects; there was a fall in the PSI after stress in all the controls. The criterion adopted for "no change" was a rise or fall in the PSI of less than 4% of the immediately preceding (pre-stress) level.

An analysis of variance of the PSI over times showed that the changes seen in the group of in-patients were not significant and changes in the group of out-patients were significant only if the analysis of variance of the PSI was carried out over the first three readings; this was probably due to the fact that the two patients showed a delayed paradoxical response, which may also account for the rapid return of the PSI to pre-stress levels in this group.

Inter-group differences in the basal level of the PSI were also noted; the in-patient group showed a lower basal PSI than the out-patient group and the difference in the mean values was significant ($t = 1.983$, $p < 0.10$); significant differences in the mean basal PSI were also seen between the group of in-patients and the controls ($t = 5.978$, $p < 0.001$) and between the group of out-patients and the group of controls ($t = 2.242$, $p < 0.05$).

Clinical Rating: The mean scores in the two patient groups on the withdrawal

and prognostic rating scales are shown in *Table 2*. Higher scores on both of these scales are indicative of a greater degree of morbidity.

TABLE 2

	Withdrawal	Prognostic Rating
In-patients	15.32	19.64
S.D.	4.97	4.50
Out-patients	11.08	14.42
S.D.	2.15	4.68

The difference in the mean scores between the two groups were significant for both the withdrawal rating scale ($t = 2.894$, $p < 0.01$) and for the prognostic rating scale ($t = 3.27$, $p < 0.01$).

Drugs: In order to assess the effects of differences in the level of drug between the two patient groups on the PSI, the mean drug levels were t-tested and the differences were found to be non-significant.

Discussion

There has been only one reported study of the PAR to stress in schizophrenic patients (Mackinnon, 1969). The findings of this experiment confirm the general notion suggested by Mackinnon that the response of the palmar sweat glands to stress in schizophrenics differs from that seen in normals. As in Mackinnon's study, the basal PSI was lower in schizophrenics than in normals and there was a tendency towards a paradoxical rise in the PSI after a self-induced stress in some schizophrenic patients.

The cause of the low PSI level in schizophrenia is not clear and notions on its significance can only be speculative; it has been suggested that there is a high correlation between the number of active sweat glands and the basal skin conductance level (Thomas and Korr, 1957) but Martin and Venables (1966) have reported a much lower correlation (0.40, $p. < 0.05$) and have emphasised that sweat glands counts are spot counts and have the added disadvantage of not including partially filled ducts, which are known to contribute significantly to the level of skin conductance — on the other hand ,however, the electrical properties of the skin are known to be derived in part from non-sudorific elements in the skin. The finding of a lower PSI in schizophrenics would suggest, however, that lower levels of skin conductance are to be found in schizophrenics than in normals; skin resistance studies by Howe (1958), Malmo and Shagass (1949a) and Zahn (1964) have been inconclusive as there has been evidence of both higher and lower levels of skin resistance in schizophrenics than in normal controls.

The salient feature in the investigation of the PAR in this study was that the anhidrosis observed in normals after a period of self-induced stress was either absent or substituted by a paradoxical increase in the number of active sweat glands in the immediate post-stress period in the group of in-patients, while the PAR in the group of out-patients was similar to that of the control group.

The group of in-patients was composed mainly of institutionalised patients in whom all attempts at rehabilitation had failed; such patients could be categorised as poor pre-morbid schizophrenics on the basis of outcome and, indeed, the mean score on the prognostic rating scale was significantly higher in this group than in the group of out-patients, who can be considered as good pre-morbid schizophrenics.

The invariant or paradoxical PAR in the patients can be taken as an index of autonomic disorganisation, and, as the findings from the rating scales suggest, it is likely that those patients who are relatively refractory to treatment and who are characterised by high chronicity, high withdrawal and a poor pre-morbid personality are also subject to some degree of automatic disorganisation.

Mackinnnon interpreted her findings as lending support to Venables's (1967) theory of failure in the inhibitory section of the reticulo-activating system in schizo-

phrenia; since the central control of sweating involves excitatory and inhibitory influences from the hypothalamus, basal ganglia, frontal and sensorimotor cortex and a host of other structures ,and in view of the effect of circulating progesterone on the PSI, it would perhaps be of value to include such structures in the formulation of a theory of imbalance among those structures concerned with the mediation of autonomic responses.

Acknowledgements

This study was carried out at Littlemore Hospital, Oxford, and financed by the Rhodes Trust and by the Nuffield Foundation. Thanks are due to Dr. F. J. Letemendia for permission to test patients under his care and for his useful advice on the experimental design; thanks are also due to Professor M. G. Gelder for his help, encouragement and advice.

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ACCIDENTAL POISONING IN CHILDREN IN MALTA

— A TEN YEAR REVIEW —

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Accidental poisoning in children is a worldwide problem. The incidence is rising in some countries (Sweetnam, 1968; McKendrick, 1960) and the mortality is not negligible. Cauchi-Inglott (1956) analysed accidents in general in Malta involving children in the home, and Cachia and Fenech (1964) reviewed the problem of kerosene poisoning and its treatment. The purpose of this paper is to analyse the problem of poisoning in Maltese children over a ten year period and present suggestions for its prevention.

Material

The case histories of children with poisoning brought to St. Luke's Hospital, which is the main civil hospital on the Island, were reviewed over a ten year period ,from January, 1959, to December, 1968, inclusive. Throughout this period 1088 cases were dealt with. The number of cases varied from 97 to 121 per year and has accounted for 7.2 to 11.1% of all admissions to the Children's Wards, which mainly deal with non-surgical cases.

The cases were classified into Medicinal Preparations, whether in tablet, liquid or other form, and Household Agents, predominantly kerosene, disinfectants and detergents.

The cases were analysed for age and sex, monthly incidence, time-lag between ingestion and arrival in hospital, the presence of any concomitant illness, the number of siblings, admission with siblings, complications and length of stay in hospital. An attempt was made to relate the distribution of cases to socio-economic status as reflected in the father's occupation.

Findings

Type of Poison

The distribution according to the classification adopted above is shown in *Table I.* The main offenders were kerosene (50% of cases), disinfectants (14%) and Aspirin/Junior Aspirin (9.5%). From 1965 to 1968 there was only one case of Aspirin poisoning while there were 65 cases of ingestion of Junior Aspirin tab-

TABLE 1

Type of Poison: Percentage of all cases

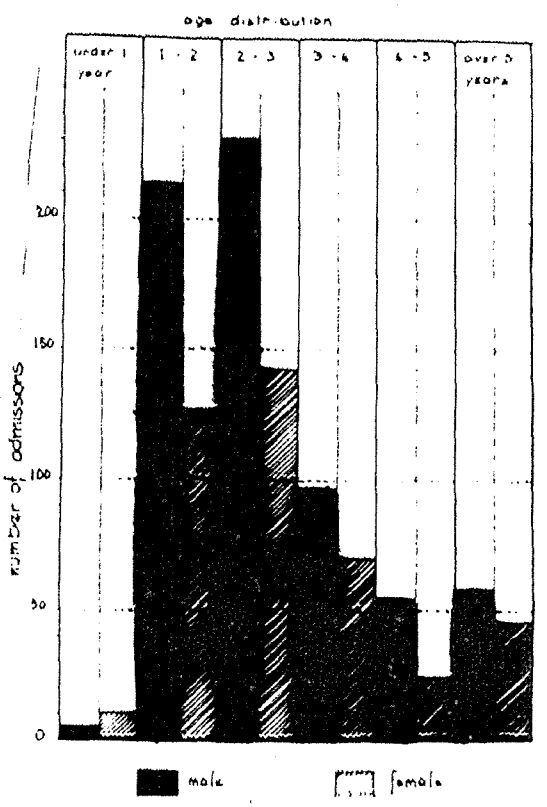
	Percentage
Medicinal	
Aspirin/Junior Aspirin	9.5
Barbiturates	2.2
Other tablets	5.5
Liquid Preparations	2.9
Other	0.1
Household	
Kerosene	49.7
Disinfectants	14.1
Insecticides	5.1
Detergents	1.9
Other	6.9
Others	
Others	2.1
All Cases	100%

lets. This rise in incidence of ingestion of flavoured Junior Aspirin has also been noted by Sweetnam (1968). Barbiturates accounted for only 2.2% of cases.

Age and Sex (Fig. 1)

Children up to 12 years of age are admitted to the Children's Wards. The youngest patient was a three-month old baby whose brother had put Surf powder into her mouth, and the oldest was an eleven-year old boy who accidentally ingested methylated spirit.

Two-thirds of the cases were in the age group 1-3 years, and males were more frequently affected than females throughout all age groups except in that under one year. This is partly accounted for by the preponderance of males under 15 years of age in the general population in Malta but it also illustrates the well-known phenomenon of the greater vulnerability of the male.



Month of Admission (Table 2)

There is an increase in the number of cases during the hot months June to September, mainly due to a greater number of cases of kerosene ingestion.

Table 2
Monthly Incidence. All Cases

J.	F.	M.	A.	M.	J.	J.	A.	S.	O.	N.	D.
59	58	55	77	81	126	162	156	109	73	78	54

Estimated time from Ingestion (Table 3)

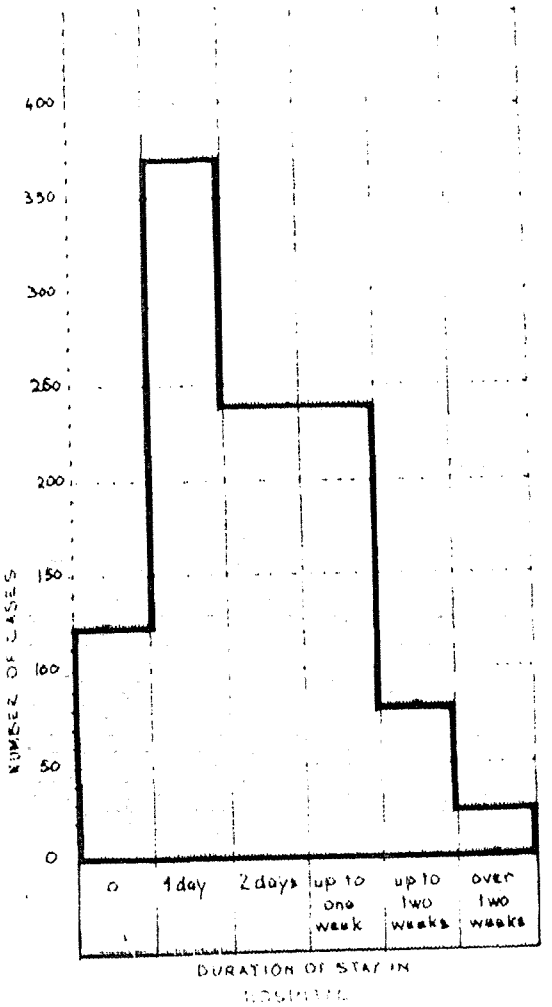
This information was available in 872 cases (83% of all cases). Just under one-half reached hospital within 30 minutes from ingestion of the poison, and a further quarter within the hour. However, even in a small island such as Malta, with good communications and an abundance of private cars, more than a quarter of the cases arrived in hospital over one hour after the accidental poisoning had taken place. This is partly due to the fact that the child is often first seen by the family doctor, who may not have been readily available, prior to referral to hospital.

Table 3
Estimated Time from Ingestion to Hospital Admission
— 872 Cases —

Under 30 mins.	30 - 60 mins.	1 - 3 hours	Over 3 hours
408	219	156	89

Duration of stay in Hospital (Fig. 2)

124 cases were admitted but were taken home at request soon after admission. 64% of the remainder were discharged within 48 hours. The longest stay



in hospital (35 days) was that of a child who was admitted in coma following ingestion of kerosene and developed severe lower respiratory tract infection; no gastric washout had been performed.

Complications (138 cases)

These were mainly lower respiratory tract infection (81%) and coma (10%). 97 cases of lower respiratory infection followed kerosene ingestion; it is the rule not to carry out gastric washout in cases of kerosene ingestion. There were only three cases of coma due to barbiturate poisoning. Other complications included convulsions, vomiting, diarrhoea, mouth ulceration (hydrochloric acid), superficial burns, conjunctivitis, haemolytic anaemia (cresol) and hypersensitivity reaction (Aspirin). There was only one death attributed to poisoning throughout the period under review. A nine month old baby had watery stools and her grandmother gave her a bottle containing what she thought was orange blossom water ("ilma żahar"), a popular remedy for colic, but it contained an insecticide. The baby developed convulsions and died two hours after admission to Hospital.

Associated Illness (22 cases)

In general there was no association between the presence of a concomitant illness and the type of poison ingested, except for bronchial asthma (ephedrine mixture, 1 case), giant urticaria (antihistamine, 1 case) and whooping cough (paracodeine, 1 case). There were only seven cases of mental deficiency recorded in the whole series.

Admission with Siblings

In 13 instances more than one child from the same household was admitted with poisoning. On one occasion, four siblings who swallowed travel sickness tablets were admitted for treatment. Three siblings were admitted for carbon monoxide poisoning, and two other siblings were overcome by petrol fumes while playing in a flooded cellar after they had upset a can of petrol.

Social Factors

Father's Occupation

This information was available in 86% of cases. In Malta in the last 10 years there has been a great socio-economic upheaval, with a marked rise in income of manual workers and improvement in living conditions. Therefore, it was not thought likely we could draw any meaningful conclusions as to socio-economic status by reference to the father's occupation. Nonetheless, manual workers

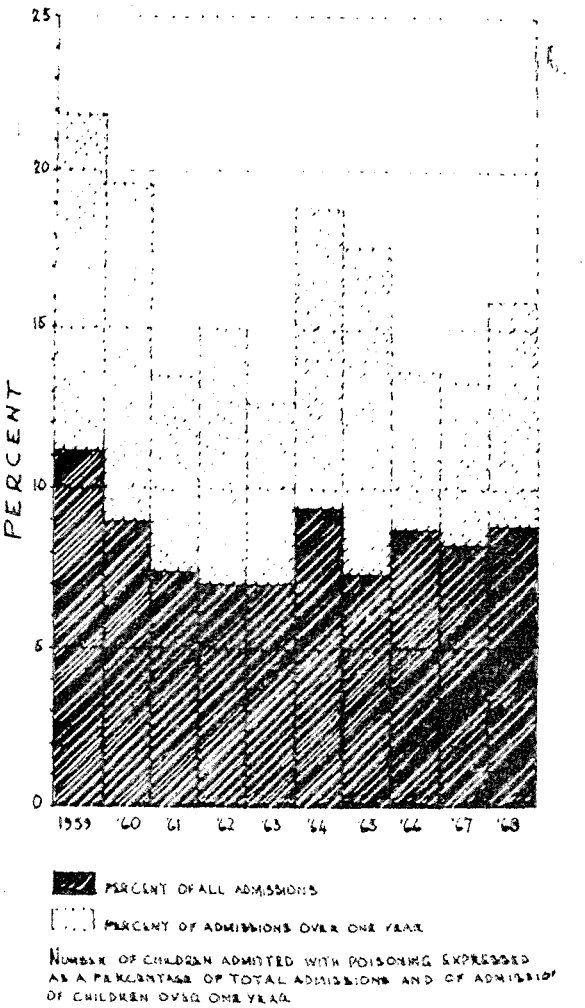
outnumbered non-manual workers by a ratio of almost four to one.

Number of Siblings

The only child in the family was the poisoned child in 22% of cases. Almost as many (21%), however, were children from large families (more than five persons, excluding parents). Indeed, an analysis of the number of children poisoned accidentally related to the number of persons in the same household showed a greater vulnerability of the child in the larger household than in the case of the only child, or the child with one or two siblings.

Problem Families (father dead, father abroad, parents separated, unmarried mother)

There were only 30 cases in this category. In some of these cases, the mother went out to work and the children were left with friends or relatives. It is unusual for the mother to go out to work in Malta. In no instance did the child come from an institution, where the accessibility of the poisons seems to be much less than in the home.



NUMBER OF CHILDREN ADMITTED WITH POISONING EXPRESSED AS A PERCENTAGE OF TOTAL ADMISSIONS AND OF ADMISSIONS OF CHILDREN OVER ONE YEAR.

Comments

The number of children admitted with poisoning accounts for 7-11% of total admissions to the children's ward at St. Luke's Hospital. However, if the infants (children under one year of age) are excluded from the number of admissions, the proportion rises to 13-22% *(see fig. 3)*. This means that poisoning is a very important cause of hospital morbidity in childhood, and if it can be prevented the the number of admissions to the children's wards could be substantially reduced. There has been no real increase in the number of children admitted with poisoningn throughout the period under review, in contrast to the trend elsewhere.

There was only one death due to poisoning in our series of 1088 cases, a mortality rate of less than 0.1%. McKendrick (1960) gave a fatality rate of 0.4% for combined English series (777 cases) and 0.45% for pooled American series (3,100 cases). The low mortality of poisoning in children parallels the low mortality of poisoning in adults in Malta (Fenech and Grech, 1970).

The public should be made aware that accidental poisoning in children is largely preventable. Admission to hospital, which more often than not is necessary for proper observation and treatment, causes avoidable distress to both the child and the parents. The child from one to to three years old is especially vulnerable, and is notoriously intolerant to separation from the mother. We feel that it is not futile to reiterate the fact that everything

accessible to children, whether a medicinal preparation or a potentially harmful household agent, should be regarded as a possible danger to the exploring child. These articles should be kept out of reach and under lock and key if possible.

The child who has ingested a potentially harmful substance should have the benefit of medical help without delay. In the Casualty Department there should be available skilled help and advice for the management of poisoning. Emergency treatment can be life-saving in selected cases. A list of non-toxic household agents, such as chalk, ink, etc., should be readily available so that the parents could be suitably reassured and admission avoided if possible. (Mofenson and Greensheer, 1970). Such information should also be available to general practitioners if it is requested.

About 50% of all cases of poisoning in children were due to kerosene ingestion. In almost all cases, the kerosene was drunk from a soft drinks or wine bottle. In only a few instances was the kerosene drunk from a can. We believe that the incidence of kerosene poisoning can be drastically reduced by urging all housewives to store kerosene in cans with a screw cap. If this fact were sufficiently publicised, through the usual media, the number of admissions of cases of poisoning in children could be reduced by almost one half.

Acknowledgements

We would like to thank Dr. T. J. Agius Ferrante and Dr. E. A. Cachia for permission to study the cases admitted under their care and Miss C. Tonna for secretarial help.

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THE DOCTOR AND THE STAGE

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This is a slightly abriged version of the St. Luke's Day Lecture delivered to the Malta Branch of the British Medical Association on the 17th October 1970 at the Medical School of the Royal University of Malta.

"He must have a clean appearance, and wear good clothes, using a sweet-smelling scent, which should be a totally unsuspicious perfume... In facial expression he should be controlled but not grim. For grimness seems to indicate harshness and a hatred of mankind, while a man who bursts into guffaws and is too cheerful is considered vulgar and vulgarity especially should be avoided." This advice by Hippocrates to the budding doctor makes a startling contrast with a speech in *The dumb lady,* a play by the 17th century dramatist John Lacy, a speech said by an old doctor to a physician on the threshold of his career: "First, have always a grave, busy face, as if you were still in great care for some great person's health, though your meditations truly known are only employed in casting where to eat that day. Secondly, be sure you keep the church strictly on Sundays, and in the middle of the sermon let your man fetch you out in great haste, as if it were to a patient. Then have your small agent to hire forty porters a day to leave impertinent notes at your house, and let them knock as if it were upon life and death. These things the world takes notice of, and you're cried up for a man of great practice, and there's your business done.....".

The contrast between these two pieces of advice is the contrast between a worthy preceptor formulating what he considers to be a correct bedside manner, on the one hand, and a materialistic adviser for whom the medical profession is just another way of earning money and must therefore be approached in the same spirit as the selling of merchandise, on the other hand. The contrast is great, but both sets of advice have something in common. Both insist on the doctor's need to do some play-acting, in order to create a suitable type of public image. This theatrical element, which the medical profession shares with other professions, notably the legal one, has been commented upon by perceptive men throughout the ages. Such men have also observed that the physician and the surgeon, in spite of the dogmatism and high claims of some of them, have their failures as well as their successes ,and that in the long run the doctor must inevitably lose his battle. A highly cynical ballad of the 18th century is clearly the fruit of this kind of observation:

"I, John Lettsom,
Blisters, bleeds and sweats 'em;
If after that they please to die,
I, John, lets 'em."

In the past, when rascally and incompetent doctors seem to have been very common, some observed that a sick doctor rarely tried to cure himself with his own prescriptions, or, as Rabelais put it, "Our bodies we commit to the physicians, who never themselves take any physic."

Moreover, as in other professions, there have always been doctors, competent or incompetent, whose venality has been notable, and indeed notably at variance with the nobility of the medical ideal. The case against the venality, both real and imagined, of the medical profession has never been put as devastatingly as in G. B. Shaw's outrageous preface to his play, *The doctor's dilemma,* a very long essay from which I shall quote just a few sentences: "That any sane nation, having observed that you could provide for the supply of bread by giving bakers a pecuniary interest in baking for you,

should go on to give a surgeon a pecunary interest in cutting off your leg, is enough to make one despair of political humanity. But that is precisely what we have done. And the more appalling the mutilation, the more the mutilation is paid. He who corrects the in-growing toenail receives a few shillings: he who cuts your inside out receives hundreds of guineas, except when he does it to a poor person for practice." Obviously, Shaw is being unfair, though one cannot just dismiss him, but the passage is important because it shows what is often behind the thinking of the outsider who is looking at the medical profession Now most dramatists have been non-medical — the most eminent exception being Anton Chekhov — so when we examine the doctor as seen by dramatists down the ages, we are really seeing a series of laymen's views, prejudices and all, and we must also remember that until comparatively recent times, some of the very foundations of medicine were unscientific and at times the frontiers between the trained doctor and the quack were not always clear.

The earliest European drama is the Greek, but I must confess my failure to find doctors as characters in both Greek and Latin drama, with the exception of one in the *Manaechmi* of Plautus, the play on which Shakespeare was to base his *Comedy of errors*. In this play Sosicles is mistaken for his twin Menaechmus and reacts angrily, so angrily in fact that he is thought to be mad. This causes Manaechmus's father-in-law to send for a doctor. With his flair for realistic portrayal, Plautus makes the father-in-law, like anyone very anxious to see the doctor arrive, moan that the doctor is taking an unconscionable time to come: "My bottom's numb with sitting, and my eyes sore with watching out for him. Hurry up, man; can't you move faster than an insect?" The doctor himself has bedside manners that verge on the adulatory; he even promises to sigh over his patient every minute of the day. He is the pompous type who does not stop to ask himself whether his jargon will be understood by his patients and is probably out to impress. When he asks the father-in-law whether it is a case of possession or hallucination, and whether there are "any symptoms of lethargy or hydropsical condition", he gets the answer he deserves: "I've brought you here to tell me that, and to cure him." The unlucky man is then presented not with Sosicles but with the other twin, Menaechmus, and all his solicitous questions get impatient answers, so that he immediately diagnoses a mental disturbance and says, "It'll take bushels of hellebore to get the better of this malady." The doctor's scene is not very long, but it is enough to establish him as a three-dimensional character who is funny without being grotesque.

The long stretch of the Middle Ages is a poor period for drama in all European countries, and the drama that one does find is either based on episodes from the Bible or else has abstractions and not real men and women for its characters, so it is not surprising that I have been unable to discover any doctors in mediaeval drama, though a more thorough search than I have been able to carry out may reveal one or two. I hope you will therefore forgive me for drawing your attention to the portrait of a doctor drawn by a writer who was not, from a technical point of view, a dramatist but whose rich genius had a strong element of the dramatic in it. In the prologue to *The Canterbury* Tales Geoffrey Chaucer gives a balanced characterisation of a Doctor of Physic, whom he praises for his knowledge of etiology and of all the classical literature on medicine, as well as his skill in curing, but whose fruitful alliance with the apothecaries and love of gold he openly satirises. I shall quote some couplets from Chaucer's description:

"He knew the cause of everich maladye,
Were it of hoot or cold, or moiste,
or drye

.....

The cause y-knowe, and of his harm
the rote,
Anan he yaf the seke man his bote.
Ful redy hadde he his apothecaries,
To sende him drogges and his letuaries,

For ech of hem made other for to winne;
Hir frendschipe nas nat newe to beginne.
.....
Of his diete mesurable was he,
For it was of no superfluitee.
But of greet norissing and digestible.
His studie was but litel on the bible.
.....
He kepte that he wan in pestilence.
For gold in phisik is a cordial,
Therefore he lovede gold in special."

Like Plautus's doctor, Chaucer's is viewed critically and gets what the poet believes to be his due, but he is not caricatured. He is far from being the grotesque figure we shall find in a number of plays written in later times; indeed what is most admirable about Chaucer's description is its great restraint, seen at its best in the ironic closing couplet.

The Renaissance brought about great advances in medicine, but many doctors were slow to keep abreast of them, their knowledge of sonorous aphorisms in Greek and Latin being often far superior to their ability to prescribe the necessary medical remedies. Naturally this aroused the laughter and scorn of the extraordinary intellectuals which this period produced. One should not therefore be surprised to find in Italy, the cradle of European intellectual rebirth, such an acute-brained and cynical man as Nicolò Machiavelli satirising the medical profession in his *La mandragola* (The mandrake), the most brilliant example of the Italian *commedia erudita* of the 16th century.

Like Machiavelli, Christopher Marlowe could write a bitter type of comedy. *The Jew of Malta,* for instance, contains satire as biting as the Italian dramatist's. But Marlowe was above all a writer of tragedy. The play that made his name, *Tamburlaine,* is tragedy of an epic, highly rhetorical type which describes very colourfully the irresistible career of the great Scythian emperor. When, towards the end of this play's Part 2, Marlowe comes to Tamburlaine's death, he naturally has to treat it as heroically as his life. We therefore see the emperor's physician telling him of his sickness in the typical grand Marlowian verse, although a modern audience would certainly be moved to smile, if not to laugh, by the opening reference to Tamburlaine's water:

"I view'd your urine, and the hypostasis
Thick and obscure, doth make your danger great:
Your veins are full of accidental heat
Whereby the moisture of your blood is dried:
The humidum and calor, which some hold
Is not a parcel of the elements,
But of a substance more divine and pure,
Is almost clean extinguished and spent,
Which, being the cause of life, imports your death.
Besides, my lord, this day is critical,
Dangerous to those whose crisis is as yours:
Your artiers, which amongst the veins convey
The lively spirits which the heart engenders,
Are parched and void of spirit, that the soul,
Wanting those organons by which it moves,
Cannot endure, by argument of art."

It is clear from this speech that even in the late 16th century, some doctors were still ready to confuse medicine with astrology. Not that Marlowe is satirising him; far from it. This doctor is in fact being presented with all the dignity which a royal physician acquires by reflection from his illustrious patient.

But Marlowe's doctor, as one can see by his terminology, is a traditionalist, a Galenist, who would naturally have scorned the new empirical school which had evolved during the Renaissance. As Herbert Silvette says in *The doctor on the stage* (Knorville 1967) during the 17th century – to which one can add the late 16th century – one finds "both ancient and modern opinion coexistent in some of the popular literature of the day, but with this distinction: the old is introduced with the deference usually paid to hereditary knowledge, while the new is treated as a fit subject for satire and farce."

It is a pity that Shakespeare never gave a medical man a very important part in his plays. The most notable Shakespearean character with a knowledge of medicine is Helena, the heroine of one of the dark comedies, *All's well that ends well,* who is not technically a doctor but the daughter of a lately-deceased and very famous doctor from whom she seems to have learned a considerable amount about medicine. Helena puts her knowledge to excellent use, for the King of France is grievously ill, of a fistula Shakespeare tells us, and all his doctors have pronounced him incurable.

Among her father's papers, the beautiful Helena has found directions for the cure of the disease from which the King is suffering, so she goes to Paris where she can also see again the Count Bertrand de Rousillon, her patroness's son, with whom she is in love. When the purpose of Helena's visit is announced to the King, not surprisingly he remains sceptical at first — after all the girl was not an FRCP or even a humble MD — but Helena presses him hard and promises a cure within forty-eight hours. I feel sure that no other doctor, off-stage or on it, ever said "You will be cured within two days" in such an elaborate fashion:

"Ere twice the horses of the sun shall bring
Their fiery torches his diurnal ring:
Ere twice in murk and occidental damp
Moist Hesperus hath quenched his sleepy lamp,
Or four-and-twenty times the pilot's glass
Hath told the thievish minutes how they pass,
What is infirm from your sound parts shall fly,
Health shall live free, and weakness freely die."

If the cure fails, Helena will die, but if she succeeds, her fee is to be a very unusual one: the right to have any husband she may choose from among the king's subjects. The king is cured, Helena chooses the Count Bertrand as her husband. Not surprisingly, Bertrand does not like the idea of having a wife forced on him, but his main objection to her shows the lowly social status of the physician at the time:

"I know her well;
She had her breeding at my father's charge:
A poor physician's daughter my wife! Disdain
Rather corrupt me ever!"

Poor Helena has to go through a good deal of unhappiness before she gets her full fee.

The doctor in *Macbeth* is a very minor character who appears briefly in two scenes, one of them the famous sleep-walking scene. He is a very sensible doctor who realises that Lady Macbeth's illness is psychological not physical, or as he puts it, "she is troubled with thick-coming fancies / That keep her from her rest." He also knows that Lady Macbeth can cure herself: "Therein the patient/ Must minister to himself." Macbeth flies into one of his insane rages, and when he leaves the stage, the doctor wryly remarks: "Were I from Dunsinane away and clear/Profit again should hardly draw me near." This impression of sound commonsense has already been created by his behaviour during the sleep-walking scene, in which Shakespeare adds something to the doctor's characterisation in almost every speech he utters, such as the curiosity not due merely to professional reasons which makes him urge the Gentlewoman who waits on Lady Macbeth to tell him what she has overheard her mistress mutter during her sleep-walking, and which make him jot down what he himself hears Lady Macbeth say. The terrible revelations of what he overhears leads him to sum the situation up epigrammatically: "More needs she the divine than the physician." His modern counterpart would have suggested a psychiatrist rather than a theologian, but the diagnosis would have been almost identical.

Cornelius, a character in the late comedy *Cymbeline* is another Shakespearean doctor I shall glance at. He appears in just

one scene where he is asked by the villanous queen to suppy her with poison. Unlike many of the doctors who briefly appear in Elizabethan and Jacobean plays, Cornelius is not an unscrupulous assistant of royal murderers. In fact he is suspicious of the queen's purposes and does his duty by asking her bluntly why she wants it:

"But I beseech your grace, without
offence, —
My conscience bids me ask —
wherefore you have
Commanded of me these most
poisonous compounds..."

Unlike some professional men, medical or non-medical, he does not satisfy his conscience by putting a formal question and accepting the answer, however unconvincing, that he gets. What he does is to give the queen a drug which produces the outward symptoms of death and leaves the stage satisfied with himself, for as he says in an aside, he is "the truer/So to be false to her."

Another admirable doctor can be found in Thomas Dekker's *Match me in London*. Don John, the King of Spain's brother, suddenly asks his doctor whether he is prepared to poison a man. The poor doctor replies, "Your lordship's merry," and when he learns that the victim is to be the queen's father, he replies, " 'Tis my certain death to do it" and gets the brutal rejoinder, "And thy certain death to deny it." Like Cornelius in *Cymbeline*, however, he gives the victim only a drug that puts him to sleep, and then goes to confess the matter to the king. The doctor, I must remark, does not get the slightest reward, or even a word of thanks. That may be why many of the doctors in the plays of this period are villains.

Very different are the effects of another great man's requests to a physician in Ben Jonson's *Sejanus*. In the first act of this tragedy, we find the Machiavellian Sejanus trying to cajole the physician Eudemus into betraying profession secrets. He starts off by asking him which of his women patients "is the most pleasant lady in her physic," a question to which Eudemus bashfully refuses to answer. Sejamus reacts coarsely:

"Why, sir, I do not ask you of their
urines,
Whose smells most violet? or whose
siege is best?
Or who makes hardest faces on her
stool?"

Eudemus, however, remains cautious, and even when Sejanus openly offers him a bribe, he makes the classic reply:

"But, good my lord, if I should thus
betray
The counsels of my patients, and a
lady's
Of her high place and worth; what might
your lordship,
Who presently are to trust me with
your own,
Judge of my faith?"

We soon realise, however, that Eudemus is no Cornelius. When Sejanus offers to make him "a man made to make counsuls," he becomes eager to arrange an assignment in his own garden between Sejanus and his patient Livia, and even prepares a poison for the killing of Livia's husband. As Sejanus says of Eudemus, "ambition makes more trusty slaves than need."

Possibly even more villainous than Eudemus is Lecure in *Thierry and Theodoret*, a play by Beaumont and Fletcher. Lecure is physician to Brunhalt, an evil and lascivious queen-mother who has been expelled from the Court of one of her sons, and goes to make mischief in that of her other son, Thierry. When Thierry is about to get married, Brunhalt is afraid that her influence will disappear, so the unscrupulous Lecure suggests a way of wrecking the marriage on the marriage night itself. He will give Thierry a potion, he says:

"Which when given unto him on the
bridal night
Shall for five days so rob his faculties
Of all ability to pay that duty

Which new-made wives expect, that
she shall swear
She is not matched to a man."

The plan succeeds all too well, but Brunhalt and her cronies now want to kill Thierry. Lecure again proves himself useful. He gives Thierry a poisoned handkerchief which has the horrible effect of preventing Thierry from closing his eyes and soon brings about his painful death. The wicked, however, also come to a sticky end, though Lecure dies a somewhat unsatisfactory death by his own hand offstage. ...

Another bad doctor, a catspaw in the hands of the evil Brachiano and Flamineo, is Doctor Julio in Webster's dark tragedy, *The white devil.* I shall not bother you with what he is told to do, but perhaps I should quote what Flamineo, the Machiavellian villain who hires him, says about him to his face: "A poor quack-salving knave, my lord; one that should have been lashed for 's lechery, but that he confessed a judgement, had an execution laid upon him, and so put the whip to a non plus..... He will shoot pills into a man's guts shall make them have more ventages than a cornet or lamprev: he will poison a kiss....." The rest of the speech is so coarse, that I will refrain from quoting it. As you can see, however, from this speech and from what we have said about other villainous doctors, these Renaissance physicians certainly lived a very strenuous life. The impression one gets from these plays is that they did everything except cure people.

It is with some sense of relief that one turns from these rascals to other doctors who not only refrain from misusing their profession but also actively practise it for the good of their patients. One good example is Friar Anselmo, a character in the first part of Thomas Dekker's *The honest whore.* This friar is the superintendent of Bethlehem Monastery supposedly in Milan, although it was obviously meant to remind contemporary audiences of the Bethlehem hospital in London, the famous Bedlam. Friar Anselmo is a good man interested in the welfare of his patients, though naturally his treatment of them is the one thought to be suitable for mental patients at the time, which included chaining, whipping and dieting. As the friar says of his patients:

"They must be used like children,
pleased with toys,
And anon whipped for their unruliness."

And one of his former patients says: "I was a mad wag myself here, once, but I thank Father Anselmo, he lashed me into my right mind again." Much subtler are the methods of Dr. Hughball, in Richard Brome's *The antipodes,* though his patients seem to be neurotic and are far from being violently insane. Hughball uses a psychological shock treatment. Indeed, one of the other characters thus says of him:

"And not so much by bodily physic (no!
He sends few recipes to th' apothecaries)
As medicine of the mind, which he
infuses
So skilfully, yet by familiar ways,
That it begets both wonder and delight
In his observers, while the stupid patient
Finds health at unawares."

One of his patients is Peregrine who has a morbid restlessness which makes him yearn to be travelling all the time. Hughball cures him by creating an environment, with the aid of a company of actors, which deceives Peregrine into thinking that he has been transported to the antipodes, where everything is the reverse of what it is in Britain; for instance, rogues are rewarded, lawyers are in rags and poets in fine clothes. This topsy-turveydom leads Peregrine to conclude that there is no place like home. Another patient, who is a very jealous husband, is cured by being made to witness at night a feigned attempted seduction of his wife, who emerges from the encounter with flying colours. This sounds like, and is, the application of elementary psychology, but at least one is here seeing a doctor attempting a cure which is not based on rigid formulae.

In the second half of the seventeenth century, the greatest dramatist interested in the medical profession is not an Englishman but the French Jean Baptiste Moliere. He and George Bernard Shaw must be reckoned to be of all dramatists the two who have detested doctors most. For Moliere doctors are but quacks who have achieved respectability, whose only ethical concern is to exclude other doctors who do not belong to their own confraternity, who do not care a hang for their patients but care a great deal for their fees. This little dialogue from *M. de Porceaugnac* already gives an idea of the scorn felt by Moliere. A physician is asking a countryman about a relative who is a patient of his:

Phys.: How many times has he been blooded?

Countr.: Fifteen times, sir, — within this fortnight.

Phys.: And does he not mend?

Countr.: No, sir.

Phys.: That's a sign his distemper is not in his blood."

In another play, *L'amour medecin* (Love the best doctor) again the doctors are not spared, the emphasis being on what Moliere regards as being their supreme cynicism. In the play, Sganarelle's daughter, Lucinda, pretends to be ill so that her lover, of whom her father disapproves, may visit her disguised as a doctor. But first four real doctors are summoned. We are prepared for their entrance by what the maid says: "What do you want with four doctors, master? Isn't one enough to kill the girl off?" When the doctors arrive, the maid tells one of them that another patient of his has died. The doctor, however, refuse to believe her: "It is quite out of the question. Hippocrates says that such maladies last either 14 or 21 days, and it is only 6 days since he fell ill." This rigid dogmatism in the face of facts was something that Moliere could not stomach. The doctors are left alone to hold their consultation. They talk and talk..... about the excellence of their horses or about a medical controversy utterly unconnected with Lucinda's case. By the way, they still have not even seen their patient. The whole dialogue is of course a caricature, but some of it rings true. One of them says of a Dr. Artimius: "Of course his treatment, we know, killed the patient, and Theophraste's ideas might have saved him, but Theophraste was in the wrong all the same. He should not have disputed the diagnosis of a senior colleague." The same man narrates how he quarrelled with a doctor who did not belong to the same faculty, a quarrel which went on until the neglected patient died. His comment is: "When a man's dead, he's dead and that's all it amounts to, but a point of etiquette neglected may seriously prejudice the welfare of the entire medical profession." When the doctors are finally asked for their opinion, they give it without having examined Lucinde. They prescribe anodynes, bleedings and purgings, but they will not commit themselves about the certainty of a cure. Lucinda may, in spite of everything, die but, to quote one of them, "Far better die according to rules then live on in spite of them."

Before leaving Moliere, I must mention one more play of his, *Le medecin malgre lui* (A doctor against his own will) in which Sganarelle is tricked into impersonating a doctor and is used by Moliere to parody medical jargon. I shall quote one speech:

"Now as these vapours... pass along the left side, where the liver is, to the right side, where the heart is, one finds that the lung, which in Latin is called annyan, being connected with the brain, which in Greek is called nasmus, through the hollow vein, which in Hebrew in called cubile, encounters these vapours as they pass along and these fill the ventricles of the scapula, and since these vapours... I beg you to follow my argument... and since these vapours have a certain malignity... which is caused by the secretion of humours engendered in the concavity of the diaphragm, the result is that these vapours... ossabandus, nequeys, nequer, potarinum, quippa milus. That is the real cause of your daughter's dumbness." And

when the girl's father protests that the liver is not on the left side and the heart not on the right, Sganarelle is not at a loss, "Yes, that is what it was like once, but we have changed all that, and nowadays we practise medicine in an entirely new fashion." It is, I suppose, a remark which all doctors make at least once in their lifetime, either defiantly or defensively.

The last word on Moliere was said by Shaw: "Until there is a practicable alternative to blind trust in the doctor, the truth about this doctor is so terrible that we dare not face it. Moliere saw through the doctors; but he had to call them in just the same."

Coming to the eighteenth century, we meet one of the most genial of Italian dramatists, Carlo Goldoni, who learned much from Moliere but does not seem to have shared his views about the medical profession. In one of his best comedies, *La famiglia dell'antiquario* (The family of the antiquary), in fact he gives us a somewhat pathetic portrait of an elderly doctor who is a hanger-on in a noble household. At the end of the play, however, the doctor redeems himself by playing an important part in setting right a serious domestic trouble.

Another of Goldoni's doctors, in *Il bugiardo* (The liar), is completely different. He is a successful man with two daughters whose reputation, however, is being damaged by a slanderer. In his dismay, he cannot help using medical terminology: "Oh, wretched me! Poor house! Poor reputation! This is an illness which Hippocrates and Galen cannot teach me to heal! I shall, however, discover a system of moral medicine, which can strike at the trouble's root. The essential thing is to make haste, to prevent the illness from making too much headway and from establishing itself. Principiis obsta, sero medicina paratur." The doctor is a serious man, not quite the stereotyped heavy father, though towards the end he does threaten to send a daughter, who has behaved imprudently, to a convent. Still, he is only behaving in the way fathers were suposed to behave at the time. In this same play, we also find a medical student, Florindo, in love with Rosaura, one of the doctor's daughters. Florindo is gently caricatured by Goldoni. In one scene, where he is sent to look after Rosaura, who has fainted, he timidly touches her hand, is in raptures, and immediately swoons as well.

Another 18th century dramatist, the Irish Richard Brinsley Sheridan, gives a caricature of a doctor in his farce, *St. Patrick's Day*. The sentimental Dr Rosy helps an Irish lieutenant win the hand of Laura, whose father is strongly opposed to the match. As in the plays of Moliere and in those of other dramatists, the doctor's free entry to people's houses makes him an excellent fellow-plotter. In a soliloquy Rosy thinks nostalgically about the days when he courted his wife, and expresses himself grotesquely by means of medical imagery. He is a pompous and rhetorical man who drives even his friends crazy with his inconsequential talk. His big scene comes when he has to persuade the tyrannical father that he has been poisoned. He pretends to see black spots on the man's nose and to be unable to hear him properly. Indeed he moans over the man so much as to provoke from him the appellative of "Dr Croaker". He is hardly consoling when he says he can do nothing to cure the man, but that he will certainly see justice done on his murderer. Of course, all this is an excuse for Dr Rosy to fetch the lieutenant disguised as a German quack doctor — a trick which Sheridan borrowed from Moliere. Still, I imagine that only the ordinary doctor's still fairly low social standing even late in the 18th century can have made such a ruse acceptable to the contemporary audience.

At this point I feel I must crave your indulgence, for I must make a great leap from the late eighteenth to the second half of the 19th century. My only excuse is the relative unimportance of drama during the Romantic period, with the one great exception of Germany and the absence of medical characters from the German plays of this period I am familiar with. The second half of this century brings us to one of the greatest dramatists

of all times, the Norwegian Henrik Ibsen who revolutionised drama by making it realistic and a great tool in the hands of social reformers. His *Ghosts* has an obvious interest for the doctor, but there are no medical characters in it, so I shall draw your attention to two other plays of his, *The master builder* and *The wild duck*. In these two plays, Ibsen presents doctors as people of whom he obviously approves, practical men and spokesmen of the common sense point of view. Unlike his disciple, Shaw, whose views we have already glanced at and will examine further later on, Ibsen does not regard doctors as parasites or even as menaces to society. Dr Herdal, in *The master builder*, is a good family doctor, a friend as well as a physician. In his dealings with Solness, the master builder, he is tactful as far as possible, but does not shirk asking searching questions if he deems them necessary. He has a certain dry humour and will stand no nonsense. Solness, a married man, is infatuated by his female clerk but tries to make it sound as if it is just the other way round. He tells the doctor, "I can see that she's conscious of me when I look at her from behind. She trembles and shrinks if I just come near her. What do you think of *that*?" To which the doctor replies, "Hm — that can be explained all right." During the same conversation, Solness gives what is clearly an unconvincing explanation. The doctor does not beat about the bush and tells him, "No, I'm dashed if I understand a word." Again Solness reveals himself as being very unsure of himself He is scared stiff of the new generation which, he says, will one day come knocking at his door. The doctor, realising that in such an eventuality the danger will come not from the new generation but from within Solness himself, poo-poohs his fears: "Well, good gracious, what about it?" At this point in the play there is literally a knock at the door. The girl who enters will prove to be Solness's undoing, but the action makes it clear that this undoing has been willed unconsciously by the master builder himself.

Relling, the doctor in *The wild duck*; is not only as blunt as Herdal but also capable of throwing aside the conventions of politeness in order to save his friends from the dangerous, morbid idealism of Gregers Warle. At one point, Gregers speaks metaphorically of the stench he can smell in Hjalmar Ekdal's house. Relling immediately buts in, saying, "Excuse me, it couldn't be you yourself, I suppose, who's bringing the stench with you from the mines up there?" Relling ends by even threatening to throw Werle down the stairs. Lather he gives his diagnosis of what is wrong with Werle, "Acute inflammation of the conscience" which he considers to be "a national disease; but it only breaks out sporadically." Relling's fears about Werle prove to be only too well-founded, and all his efforts to warn Hialmar are futile.

The other very great dramatist of the late 19th century is our doctor dramatist, Chekhov. Oddly enough — but perhaps not so oddly — Chekhov's three highly interesting medical characters (I am ignoring Chebutykin in *The three sisters)* are not admirable persons, and one of them almost qualifies for the post of villain of the piece. This unpleasant fellow is Yevgenij Kostantinovich Lvov, a character in Chekov's first full-length play, *Ivanov*. Lvov is a young, newly-qualified doctor, an idealist as dangerous as the non-medical Werle in Ibsen's *The wild duck*.

Dorn, in *The seagull*, is different in most respects from Lvov. He is fifty-three and, far from being an idealist, he is a cynic about everything, including his profession. Perhaps the listless rural society in which he finds himself — remember this was the last period of the Czar's rule in Russia — had squeezed out of him any enthusiasm he may have had once, but his *malaise* seems to have even deeper roots.

His attitude to medicine emerges beautifully in a couple of scenes. The old Sorin, who is unwell, would like some medical treatment, but Dorn's reaction is, "Treatment! At sixty!" When pressed, he grudgingly says, "Oh, all right then, take some valerian drops." In a later Act, Sorin is very ill and complains that he is being neglected by Dorn. Dorn's reply shows the

same lack of interest as before: "Well, what would you like to have? Valerian drops? Soda? Quinine?" Dorn, who feels that life is a tremendous cheat, cannot fathom how Sorin wishes to hold on to it. The only help he tries to give the old man is to exhort him to suppress the fear of death.

The most fascinating of Chekhov's doctors is certainly Astrov in *Uncle Vania.* He is a complex character, half-way between Lvov and Dorn both in age and in temperament. In his late thirties, his handsome looks have been impaired by sheer hard work and by his heavy drinking. He himself says that having lived for so many years among the queer people of his province, he himself has become a little queer himself; his feelings have grown duller, and he does not love anyone. Because he knows he is a heavy drinker, he is troubled by the death of one of his patients during an operation. He has lost the capacity to love anyone, his one great passion being for inanimate objects: trees

In the plays of George Bernard Shaw, the attitude to doctors marks a return to the bitter satire of Moliere. Even if some of Shaw's medical characters are more complex than Moliere's, there is a caricatural element in practically all of them. Shaw fired his first broadside in an early play, *The philanderer,* in which we find an eminent physician, Dr Paramore, who has made his name as the discoverer of a liver disease named after him. Colonel Craven one of Paramore's patients, has had the disease diagnosed and has been given only a year to live. In the second Act Paramore has been reading the B.M.J. offstage. Suddenly he come in, with an expression of despair on his face. He is asked whether he has received bad news and replies, "Terrible news! Fatal news!" We find out that he has read in the B.M.J. that Paramore's disease has now been discovered not to be a disease at all. Not unnaturally Colonel Craven is both jubilant and hurt that Paramore should regard this as horrible news, but Paramore is only rude to him. Shaw also satirises the grumbling of all research workers that they do not get enough funds for their research. While he had been given only three dogs and a monkey on which to experiment, in "enlightened republican France" one doctor had been given two hundred monkeys, and another three hundred dogs at three francs apiece to do research on Paramore's disease. In a fit of rage, Paramore threatens to rediscover the disease, because, as he says, "I know it exists; I feel it; and I'll prove it if I have to experiment on every mortal animal that's got a liver at all."

In *The doctor's dilemma,* Shaw's criticism of doctors and medical practice is dominant, and in fact Shaw wrote a very long preface to the play when he published it. In this preface, Shaw comments indignantly on the different opinions held by doctors, differences which do not prevent them from supporting each other in public. He writes: "Yet the two guinea man never thinks that the five shilling man is right: if he did, he would be understood as confessing to an overcharge of £1. 17." This notwithstanding, in public doctors seem to agree, though, he adds, "Even the layman has to be taught that infallibility is not quite infallible, because there are two qualities of it to be had at two prices." Doctors, Shaw says, dare not accuse each other of malpractice because they are not sufficiently sure of their own opinions, and the effect is "to make the medical profession a conspiracy to hide its shortcomings."

Thus in *The doctor's dilemma* we find that Sir Colenso and his colleagues, though they are strongly of the opinion that an eminent colleague of theirs is constantly endangering patients by his ignorance, do not dream of denouncing him publicly. There is an abundance of satire in the play. We thus find that Dr Scutzmacher has made a fortune as a G.P. by putting on his plate: "Advice and medicine sixpence. Cure guaranteed." Not very subtle satire, perhaps, but it clearly shows what Shaw thought about the venality of doctors. Another man, a surgeon, has, we hear from one of his colleagues, "worked hard at anatomy to find something fresh to operate on; and at last he got hold of something he calls the nuciform sac, which

he's made quite the fashion. People pay him 500 guineas to cut it out." Like Paramore's disease, however, there is a great possibility that the nuciform sac exists only in this medical man's imagination. Professional envy is beautifully satirised. Walpole, the nuciform sac man, comes to congratulate Sir Colenso on his new knighthood, but makes it clear that he is happy for Colenso as a man not as a professional, since he thinks that the medical treatment that has made Colenso famous is nothing but rot.

The doctor's dilemma is not merely a satire. It is, in fact, an unusual play for Shaw, a tragicomedy. The dilemma of the title is that faced by Sir Colenso. Whom will he save: a very good man but a worthless doctor ,or an unscrupulous rascal who happens to be a great artist? The dilemma grows greater because Sir Colenso falls in love with the artist's wife. He finally resolves it by declining to treat the artist and handing him over to an eminent but highly unscientific colleague who will in all probability kill his patient, as in fact he does. The play ends very ironically. The fifth-rate doctor whose life is saved gets out of his wretched practice and prospers in government employment, whilst Sir Colenso discovers that the beautiful widow regards him as an uninteresting middle-aged man, and has in fact remarried. This makes him exclaim: "Then I have committed a purely disinterested murder." I must add, however, that Sir Colenso's motive in "murdering", as he puts it, the artist has not been merely selfish; one strong motive has been his desire to free the wife from what he regarded as being a wretched existence. By making him discover that the woman has been happy, in spite of her husband's scoundrelly behaviour, Shaw jibes at those doctors who believe that they should regulate their patients' lives as well as their health.

When one examines the plays written in our own age, one is bewildered by the sheer number of works, works of all types: drawing-room comedies, thrillers, surrealistic plays, plays of social criticism..... Medical characters can be found in a fair number of them. Just to mention a few, there is the doctor who has committed murder in the thriller *Bonaventure,* the shrewd Scottish doctor in Brighouse's *Hobson's choice,* the alcoholic Dr Farley in N. C. Hunter's Chekhovian *A day by the sea,* the young doctor faced with the difficult task of treating a case of suspected criminal assault on a young girl in Michael Hasting's *Yes, and after.* One of the most interesting, however, is Dr Copperthwaite in *The happy haven,* a satirical black comedy by the contemporary dramatist, John Arden. This doctor is the superintendent of a home for old people, all of whom have been failures of one sort or another. He represents the efficient but fairly impersonal administrator, fully aware of the need for good public relations. Thus, in his opening speech, addressed to the audience, he is careful to point the home's amenities, using language which is a parody of publicity brochures. When towards the end of the play, the home is visited by a group of distinguished visitors, Arden again takes delight in parodying the inane commentary of administrators to visitors which all of us know all too well on similar occasions. To listen to a sample: "To the right my Operating Theatre, and ancillary departments, as you might say, perfection of function is in itself beautiful — but of course, Sir Frederick, *you* know all this already — Mr Mayor and ladies, we see over there the Sir Frederick Hapgood Ward, opened last year by Sir Frederick himself, there's a large bronze plaque in the foyer commemorating the occasion, and of course the Annigoni portrait of the late Lady Hapgood, which we account one of the Happy Haven's most treasured possessions." Copperthwaite is not just an administrator; he is also a research scientist, using the inmates as his guinea pigs, and through him Arden attacks the depersonalisation of the inmates of certain institutions. One of the inmates says of him that whilst he was glad to apologise to the captain of his football team for having failed to score, his patients are "all his worms. And he says, 'Turn, worms, turn,' and he thinks we have got no choice."

At the end of the play, they manage to get their back on him cruelly. He has

been working on the elixir of life — throughout the play all the satire is deliberately very bold — but, in spite of his having kept it secret, the inmates find out. Far from being jubilant, they are aghast. As one of them says, "We don't want to die, but we none of us dare state that we want any more life." Their hostility is due mainly to their distaste for being managed all the time. One of them, a woman who has always wanted a child but has never had one, gives them the idea for their revenge. They steal some of the elixir, and during the official visit, when six of the inmates are due to be rejuvenated, they inject the doctor with his own elixir and reduce him to infancy. The childless innmate now has a child! One of the other inmates then makes a mocking speech, too long for me to quote in full, about the pleasures of existence in a home like theirs. I shall quote part of it: "But it should also be a beautiful moment because you will see how much, how very much we owe to you..... who take so much delight and interest in our welfare, and who always look after us like fathers and mothers, to watch our every step and stumble, at a time in our lives when we are, as you know, no more than little children to wander and to cry and to need nothing more in life than to be continually looked after by kind fathers and mothers....." This may be cruel and unfair to the devotion of many doctors and administrators, but it makes one think hard about whether patients may not at times be *used* as much as they are looked after.

It is a rather sour note on which to close this talk, but then, I think you will agree, many dramatists have been sour or worse about the medical profession. In our times, television, with such serials as *Dr Kildare*, may have righted the balance by their excessive sweetness, and presumably in future this will tend to be the pattern, as medicine becomes more and more scientific and obtains ever more astonishing results, and professional associations become stricter in the control of misbehaviour in their members. It is therefore unlikely that there will ever be another Moliere or another Shaw. On the other hand, the intimate relations between doctors and patients will ever supply, I imagine, material for the comic dramatist, and, moreover, also in an age where even the poorest have access to the best medical opinion, there are still and presumably there always will be patients, among whom there will be a few dramatists, who will echo the doggerel verse of the 16th century Euricius Cordus, which I am quoting in the English version given by Silvette (op. cit.):

Three faces wears the doctor: when
first sought,
An angel's — and a God's, the cure
half-wrought;
But when that cure complete, he seeks
his fee
The Devil looks then less terrible
than he.

MALTA 1865: MEDICAL BACKGROUND TO BERKELEY GEORGE ANDREW MOYNIHAN

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NOTE

A party of surgeons belonging to the travelling Moynihan Chirurgical Club, whose membership includes leading British provincial surgeons, paid a visit to the Surgical Professorial Unit of the Faculty of Medicine and Surgery of our University on the 7th and 9th May 1969.

On the 7th May a plaque was unveiled at Lord Moynihan's birthplace, St. George's Bay, near St. Julians.

This paper was read on the 8th May at the Medical School, St. Luke's Hospital, at a meeting of the Club.

You have come to Malta to commemorate in his birthplace one of the most brilliant surgeons of all time — Lord Moynihan; but to view the occasion in its proper perspective you will have to travel back in time to visualise the medical scene during Moynihan's short residence in Malta between October 1865 and December 1867.

You would have arrived in Malta by a coal-burning steamship which would berth in the Quarantine Harbour of Marsamxett in the vicinity of the Lazzaretto where you would be landed for the performance of a period of quarantine, for in those days every passenger was regarded as a potential carrier of infectious disease. Each one of you would be isolated from his companions and assigned an almost bare apartment, the only items of furniture being a chair, a table and a wooden bedstead.

You would not be permitted to leave your room or enter other apartments or receive visitors except under special surveillance. You would be allowed to communicate with your friends outside the Lazzaretto by means of letters but these would have to be first disinfected by smoking before delivery. To ensure that you adhered to these restrictions you would be watched and attended by a Health Guardian for whom, by the way, you had to provide not only his wages but also his daily meals; and you would be regaled by the sight of a dismal stone gallows nearby to remind you of the fate that awaited you if you dared to transgress the quarantine laws.

If, after a certain time you did not fall ill or die of plague or smallpox or cholera, you were granted pratique, that is you were set at liberty and allowed to roam about the Island at your pleasure.

The year 1865, however, was not a particularly attractive one for the visitor to Malta for on the 20th June cholera broke out in the Island, the epidemic reaching its peak at the beginning of August. The cause of cholera had not yet been discovered and its mode of propagation was not yet understood so that the sanitary precautions that were taken against the circumstances which were believed to provoke the disease were hardly effective at all; so much so that by the time it ended at the beginning of November, 3,000 cases, of whom more than half died, had occurred among the 134,000 inhabitants of the Maltese Islands. The figure of the Maltese physician Dr. Antonio Ghio stands out prominently against this backcloth of ignorance and suffering for he rightly in-

sisted that cholera was spread by means of excreta of infected persons and also envisaged the possibility of its transmission by apparently healthy carriers. To appreciate the significance of Dr. Ghio's remarks it is pertinent to remember that he was expressing them twenty years before Robert Koch discovered the cholera vibrio in 1884.

When the epidemic broke out in June, Mrs. Ellen Moynihan, the wife of Army Captain Andrew Moynihan and future mother of Berkeley George Andrew, was in her fifth month of pregnancy. She had been a witness to the scourge of cholera five years previously when this disease appeared on the troopship that was conveying her and her husband from India to England. She had then seen infants, children and adults succumb to the illness and being buried at sea. The cholera at Malta must have revived those memories for she again found herself right in the midst of the disease. She and her husband were living in the married quarters attached to Pembroke Camp, their house being one among a group of buildings situated at the foot of the slope from Pembroke to St. George's Bay. On the 27th July cholera appeared in the camp but it made little headway there being only eleven cases of which, however, nine ended fatally. The Moynihans escaped and in that house overlooking St. George's Bay, while the epidemic was still raging, Berkley George Andrew was born on the 2nd October, 1865.

But let us return once more to the visitor to Malta in that year 1865 and catch a glimpse of the kind of medical attention he would have received had he fallen ill and been admitted to hospital. As elsewhere in Europe, the nursing standards were very low. The attendants were ill-mannered, unreliable, untrained and illiterate but there were two redeeming features in an otherwise disheartening situation: first, the female attendants in our hospitals never descended to the depths of moral degradation and alcoholic deterioration as their counterparts abroad; and secondly, by 1865 we had began to feel the influence of the reforming zeal of Florence Nightingale who, by the way, had passed through Malta on her way to the Crimea in 1854 and who, in 1862, had been advising a Maltese Government official on our nursing requirements.

In contrast to your uncouth and ignorant nurse, your physician was cultured, fully trained and with seven years of university education behind him and with medical qualifications that were acknowleged to be of such high standards by the University of London as to entitle him to admission to its medical degree. This, of course, does not mean that you would have particularly relished the treatment you would have received at his hands; but then we must remember to judge him by the contemporary state of medical knowledge and practice. Since 1854 he had been obliged by Maltese law to prescribe his drugs in conformity with the London Pharmacopoeia and, later on, the British Pharmacopoeia. In other respects, however, the sheet anchor of treatment was the use of the leech for combatting pain in swollen parts and for the relief of congestion in inflamed organs; while in acute febrile diseases — and of these there were many — purging by castor oil and liberal blood letting were the accepted methods of therapy.

You fared no better if you needed surgical treatment. You would have had the benefit of ether anaesthesia which was introduced into Malta as early as 1847 by Sir Thomas Spencer Wells when he was on the staff of the Malta Naval Hospital but you would have had no protection against infection during operative procedures. Indeed we must recall that Joseph Lister had first used a spray of carbolic acid to sterilize objects coming in contact with the patient on the operating table exactly in 1865 — to be precise on the 12th August at the Glasgow Royal Infirmary — less than two months before Moynihan was born. The year 1865 was, therefore, for Moynihan a memorable and fateful one not only because it marks his birth and his survival through a cholera epidemic but also because without Lister's fundamental contribution to surgery in that year — the introduction of antisepsis —

there would not have been a world famous abdominal surgeon Moynihan in later years. Indeed Moynihan himself, when he had become President of the Royal College of Surgeons, acknowledged the modern surgeon's indebtedness to Lister when he declared, on the occasion of the centenary of Lister's birth, that operative procedures previously unimaginable had become matters of daily occurrence thanks to that one man — Lister.

But in our year 1865 Moynihan's rise to fame (1896-1914) was still in the distant future and the land where he was destined to achieve success and recognition was far away from Malta. Indeed he was in our Island only for the first eighteen months of his life and he happened to be born among us because his father, Captain Andrew Moynihan, was a professional soldier serving in the 2nd Battalion of the 8th the King's Regiment which was doing garrison duty in Malta at that time.

Captain Moynihan had seen active service in the Crimean War where he distinguished himself in the trenches before Sebastopol. He was wounded in many places but in spite of his injuries he succeeded in rescuing a wounded officer from the Russians though under terrific fire from them in open ground. For this daring gallantry he was awarded the Victoria Cross, a decoration that had just been instituted and which has remained the highest British honour bestowed on a soldier for bravery in the field. However, it was not the enemy's bullet but disease that brought Captain Andrew's life to a rapid and early end.

Malta was then notorious for the high incidence of fevers both among civilians and servicemen. It was one of these fevers that attacked and killed Captain Andrew on the 19th May 1867 at the age of 37 years. One of Moynihan's biographers ascribed Captain Andrew's death to undulant fever but the newspapers of the time attributed it to typhoid fever. Eight years previously Assistant Surgeon J. A. Marston, while in Malta with the Royal Artillery, had differentiated undulant from typhoid but for many years afterwards some medical men continued to regard undulant merely as a variant of typhoid fever and it was not until 1886 that Sir David Bruce, the discoverer of *Brucella melitensis* in the human spleen, afforded definite and conclusive proof that undulant fever was a disease *sui generis*. Whatever the correct diagnosis might have been in the case of Captain Andrew Moynihan, there is no reason to believe that it would have made any difference to the outcome of the illness considering the impotence of the therapeutic armamentarium of the time.

Captain Andrew Moynihan died at his residence at Floriana and was buried at Ta' Braxia Cemetery on the outskirts of the fortifications of Floriana where he had often turned out his smart body of soldiers for review. His grave — the gift of his brother officers — is still there. It is marked by a simple slab of Malta stone with a cross laid upon it and bears the dates of his birth and death, his rank and regiment.

Berkley George Andrew Moynihan visited Malta in 1932 as Lord Moynihan. It was during a hurried cruise to the Mediterranean so that he could spend only one day in the Island, but he managed to find the time to visit the house where he was born and also the grave of his father. Perhaps you would like to follow his footsteps and wend your way there — as I have done several times — to pay homage to the memory of Captain Andrew who was instrumental, through his son born in Malta, in giving to suffering humanity an outstanding surgical pioneer; and as we pause by his resting place let us recall the verses from Chapter 44 of Ecclesiasticus:

> *"Let us now praise famous men that begat us*
> *Their seed shall remain for ever and their glory shall not be blotted out.*
> *Their bodies are buried in peace; but their name liveth for evermore".*

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LOOKING BACK

THE MALTA CHOLERA EPIDEMIC IN 1837

SAVIOUR PISANI, M.D.

The cholera epidemic which reached Malta in 1837 originated in Tessory in India in July 1817. The disease spread fast reaching Calcutta on the 10th September 1818 after attacking intermediary points such as Ahmed Nugger, Poonah and Panwel. It was in Madras by October 1818. From there it spread outside India, reaching Ceylon in January 1819, Mauritius on the 29th October 1819 and Borbone in January 1820. By the year 1829 it had reached the frontier of Siberia and in 1837, after having infected more than 62,000,000 individuals, it appeared in Malta.

The credit for diagnosing it first goes to Dr. S. Axisa, the physician to the Hospital for Old People in Floriana. On the 9th June 1837 he was asked to see two inmates who were suffering from a severe illness. From a letter that he wrote on the 22nd August 1838 we learn that their main symptoms had been a thready pulse, cold skin of a livid colour, cramps and suppression of urine. These two patients were already on the point of death. On questioning it was learnt that the previous evening they had eaten only some meat and drunk some wine but by midnight they were suffering from severe vomiting, diarrhoea and hoarseness.

Dr. Axisa immediately took the necessary steps to inform the Health Authorities. His diagnosis was upheld by Dr. L. Gravagna, the Police Physician but Dr. Clarke the Inspector General to the Military Hospitals disagreed with them. Other physicians were called in. Dr. G. Portelli was of the same opinion as his Maltese colleagues but a certain Dr. Lawson maintained that this was not Asiatic Cholera but a variant of Mild Cholera.

Amidst this disagreement among physicians the disease continued to spread. The first victims of the epidemic were Paul Attard aged 80 years from Gozo and Francis Abdilla, 70 years, from Zebbug, who died, comforted by the Holy Sacraments. The following three days showed a sharp rise in cases. By noon of the 13th June 1837, 27 persons had been attacked, of whom 17 had died by then. Since by now the diagnosis had been established the inmates of the "Ospizio", 750 old and insane people were transferred to Fort Ricasoli. On the 14th June 1837 the official confirmation of the presence of the disease was published in the Malta Government Gazette:

"We regret to state that on Friday last several cases of severe illness appeared among the inmates of the Ospizio or Asylum for the aged and indigent poor at Floriana. Steps were immediately taken to examine into the nature of the disease

and according to the opinion of the principal Medical Officers, both English and Maltese, there seems to be no doubt that the patients were attacked by Cholera, which as yet has assumed an entirely sporadic character, being confined within the walls of the building. No case even of a suspicious nature has occurred in the any other part of the Island. Up to yesterday at 12 o'clock the number of persons attacked was 27, out of which 17 have died; the remainder of the inmates amounting to 750 aged men and women were in good health.

There being reason to believe that the malady may have been occasioned by a local cause the Governor has given orders for the removal of the whole establishment of the Ospizio to Fort Ricasoli who has for this reason been vacated by the troops. It is to be hoped that, by so prompt and humane a measure, the disease will be checked, the situation being isolated. Notwithstanding which His Excellency has given directions to the proper authorities to take every measure that may be thought necessary for the preservation of the public health should the disease show itself in any other part of these possessions.

In the meantime pursuant to a resolution of the Board of Health, the substance of the above mentioned circumstances is inserted in the bills of health granted to vessels clearing out from this island."

Since the disease seemed to be getting out of hand it was decided to nominate certain gentlemen to supervise the cases of cholera and to help to check its spread. The names of these gentlemen who were to compose "The Central Committee for the Supervision of Cases of Cholera" were published in the Malta Government Gazette of the 21st June 1837 though the Committee had already been working on the problem for two days. The names that appeared on the Gazette were the following:

President: Count Baldassare Sant
Baron Vincenzo Azzopardi
Dr. Clark, *Assistant Inspector of Hospitals* .....
Giuseppe Azzopardi de Baroni Gauci
Dr. L. Gravagna, *Police Physician*
Dr. Liddell, *Physician to Naval Hospitals*
Nicholas Nugent, *Treasurer to Government*
Major Ward, *Royal Engineer*
George Ward Esq., *Secretary.*

Four days later the powers with which this committee was invested were published in the Gazette:

1. The Governor or Central Committee with his approbation were empowered to issue orders at any time with a view to prevent the spread of cholera within these possessions.
2. Orders certified by the Secretary to the Central Committee were to be published in the same mode as Government Notices, and were to be received as evidence of the date and contents of such orders.
3. Penalties, amounting to no less than five pounds but not less than one pound sterling were to be incurred by those who violated such orders.
4. Non payment of fines was punishable by imprisonment (4s. corresponding to one day).
5. The Ordinance was to remain in force for one month.

The first meeting of the Committee took place on the 19th June. It was decided to hold a meeting every day at 11 a.m. and that five members would form a quorum. The next day was to show the trend which was to be followed by the Committee in its meetings. The first decision was to abandon the Quarantine restrictions currently existing in Fort Ricasoli. This decision was to be followed by another on the 24th June to the effect that anyone wanting to leave the fort could do so, provided, of course, he had relations and friends ready to take care of him.

It appears that a considerable number of inmates at Fort Ricasoli availed themselves of this offer for four days later there apeared a note in the Gazette to this effect:

"The inmates of the Ospizio who were removed to Fort Ricasoli, as we have already stated, have suffered in the great-

est degree, although within the last few days, the attacks have decreased considerably, the new cases yesterday being only six, the deaths fifteen. On the visit of H.E. to the hosital there, on Sunday evening, he was pleased to express his satisfaction at the medical arrangements which had been made for the care of the sick, and the zeal with which the two chaplains of the establishment had discharged their spiritual duties; they are now assisted by the Capuchin Fathers. None of the unfortunate victims of the disease died without the comforts of religion in their last moments. All those who were without suspicion of disease, and who had friends to assist them, have been allowed an outdoor pittance, with permission to withdraw themselves from the establishment for the present, and about 120 have already availed themselves of this humane measure adopted by H.E."

Looking back with our knowledge of the epidemiology of cholera this decision, although undoubtedly humane and though it certainly saved the lives of many of the former inmates of the Ospizio, certainly helped to spread the disease throughout the rest of the island. However, the authorities thought otherwise for it was their opinion that cholera was not a contagious disease. Thus on the 21st June the Committee was compelled to write to the Governor "to be moved to issue a notification on the subject of the mischievous reports in circulation as to the contagious nature of the prevailing epidemic". On the 21st June 1837 the following notice on the Malta Government Gazette:

Minute by His Excellency the Governor:

"His Excellency the Governor learns, with no less surprise than regret, that several individuals and amongst them some few Maltese medical practitioners, have industrially *(sic)* circulated their opinions, that the partial epidemic which has visited this island is of a decidedly contagious nature. A more cruel and unfounded doctrine cannot be promulgated, a doctrine opposed to the solemn decision of the most prominent medical men, collectively and individually, in the civilized world, and H.E. cannot but express his astonishment that these unpractised persons should presume to set up their unauthorised opinions, on occasion of such vital importance, in opposition to such high and unquestionable authority. The persistence therefore in such conduct, on the part of those in the employment of the Government, will immediately draw upon them the displeasure of H.E., and will operate as a disqualification for those who may hereafter become candidates for further situations."

This note was followed by another, dated the 22nd June, refuting the theory expounded by Dr. L. Galea, Conte Nicolo Gatt and Dr. G. Sammut that the disease was contagious. However, although the disease was not considered contagious the value of cleanliness was not disregarded by the Committee. Thus on Monday the 26th June it was resolved to keep the cellars of Valletta as clean as possible and to send a note to the Supervisor of the Markets asking him to issue an order forbidding the slaughter of the larger animals in the market.

The situation at this time was still moderately satisfactory. The Government thought it would be wise to discourage panic.

"Although the cases and deaths among the aged poor at Fort Ricasoli are so numerous it furnished no ground for despondency to the rest of the population, when it is considered that at the late period of life at which they had arrived, their impaired constitutions could not have been in a state to resist the attack of any active disease. Among the troops it will be seen that the disease has made little progress" (M.G.G. 21st June, 1837).

The Committee supervised very closely the activities of the medical profession. On the 27th June Mr. Mamo, an apothecary of the Civil Hospitals was severely admonished for distributing quills filled with quicksilver as a treatment for cholera. The chief objection of the Committee was that such quackery would not only lead to a false sense of security in the general public, making all precautions of security advocated by the

authorities seemingly futile. A phlebotomist, a certain Mr. Falzon, was admonished on the same day for failing to attend promptly to patients who required blood letting.

The line taken on the non-contagiousness of the disease was having its effects on the medical profession. A bleeder, Mr. Matrenza, who appeared before the Committee on the 29th June on charges of having refused to attend to a patient answered that he had done so because of the risk of becoming infected but now that the Committee had dictated otherwise he would have no objection to bleed these patients.

However, other practitioners were not so easily persuaded. One of these was Dr. G. B. Saydon of No. 3 Std. Nuova, Cospicua, who appearing before the council on the 12th July maintained that he was an uncompromising contagionist. Therefore the Commission was forced to quote authorities on the subject. A typical note appeared in the Gazette of the 28th June, 1837:

"The undersigned physicians and surgeons of the Hotel Dieu think it their duty to declare, in the interest of truth, that although up to the present time, the hospital has received the greatest number of persons affected with cholera, they have not observed any circumstance which authorises them to suspect that the disease is contagious.' '

Signed: Petit, Husson, Sanson, Magendie, Hanon, etc.

Done at the Hotel Dieu, Paris, 31st March, 1832.

Meanwhile the state of Valletta was causing a lot of concern. It was proposed to keep two dispensaries open at points as far removed from each other as possible during the night. The following roster was finally agreed upon:

1st night — Drs. Fenech and Duclos Std. Reale
2nd night — Drs. Garzini Std. Teatro and Dupont Std. Mercanti
3rd night — Drs. Parnis Std. Teatro and Portelli Std. Mercanti
4th night — Drs. Ricardi Std. Teatro and Stilon Std. Giovanni
5th night — Drs. Biancardi Std. Teatro and Gatt Std. Giovanni
6th night — Drs. Engerer Std. Forni and Aquilina Std. Paolo

The state of the Mandraggio was also worrying the Committee for on the 1st July a memorandum was sent to keep the place as free from disease as possible. Two days later another was sent to prevent sick people from the villages from using the hospitals of the cities. The arguments used were that the transport of such sick patients would certainly lead to their death and the accumulation of large numbers of sick people in the cities would certainly lead to a greater spread of the disease.

The state of Senglea was hardly better for by the 30th June the Archpriest of that city was informing the authorities that he had only 19 more empty tombs and if the disease was to continue he proposed the opening of the ancient plague burial ground. He also complained of a complete absence of phlebotomists and exhorted the authorities to send medical supplies to the afflicted city.

As the incidence of the epidemic reached its climax it was appreciated that the poor and those of low physique were the worst affected. Therefore a committee composed of 21 members under the presidency of Rear Admiral Sir Thomas Briggs was elected for the "Relief of the Destitute Poor". It was decided that:

"The Committee acting on the opinion of the medical profession that one of the best preventives against attacks of cholera is a regulated subsistence on wholesome food, have resolved that a subscription be opened for the purpose of supplying the destitute poor therewith and also for the purpose of relieving them in any such other manner as the committee may deem expedient. It is however to be clarified that the extensive prevalence of the epidemic under which the island is suffering is the only reason for opening this subscription and that as soon as the disease

TABLE 4
Incidence of cholera in the island of Gozo during the epidemic

MONTH	ATTACKED	DIED	CURED
July	532	187	181
August	220	137	241
September	57	42	-
Totals	809	366	422

The official thanksgiving for the restoration of the public health took place on the 23rd October when a Solemn Service and "Te Deum" were celebrated in the church of St. John. The Archbishop with the Chapter of the Cathedral officiated at the ceremony which was attended by a large congregation including the elite of the island amongst them the Governor, the Naval Commander-in-Chief, H.M. Judges and Rear Admiral Briggs.

Acknowledgement

I would like to thank the staff of the Royal Malta Library without whose services this work would have been impossible.

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A NOTE ON AN OLD MANDIBLE

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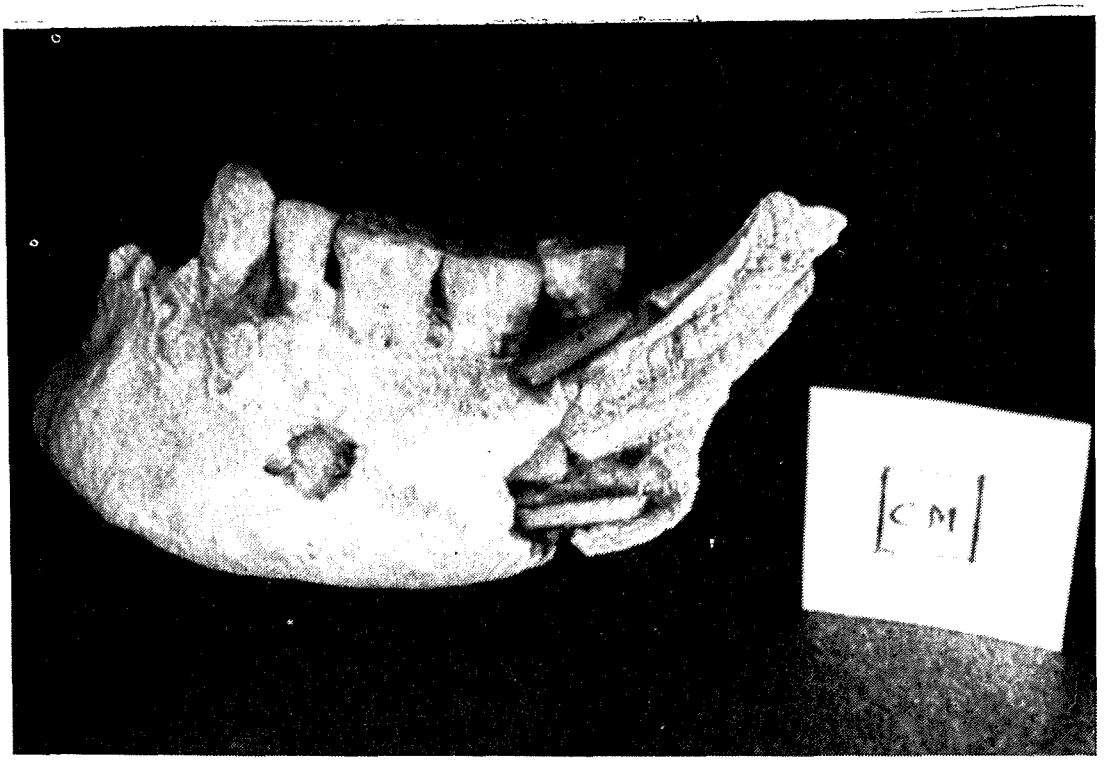
Part of a very old human mandible was brought to my attention. I was informed that it had been found with other bones "in a sort of small chamber" (probably an ancient rock tomb) while a shelter was being dug during the second world war. It shows certain interesting characteristics and I here describe its salient features.

It is in a fair state of preservation. When brought to me, it was still covered with a thin layer of sediment and this probably prevented further disintegration through the centuries.

When a human being dies, the soft parts undergo rapid dissolution, but the bones, since they are composed largely of an inorganic matrix of lime salts, may remain intact for a time. However, if they happen to be fairly quickly covered up by layers of sediment (such as particles of limestone or sand) and in some way sealed off and protected from the destructive effects of weathering or from the depredations of carrion eaters, they may remain preserved for thousands of years. A dry environment also further helps preservation. Even more resistant to destruction after death are the teeth, composed as they are of the most durable tissues of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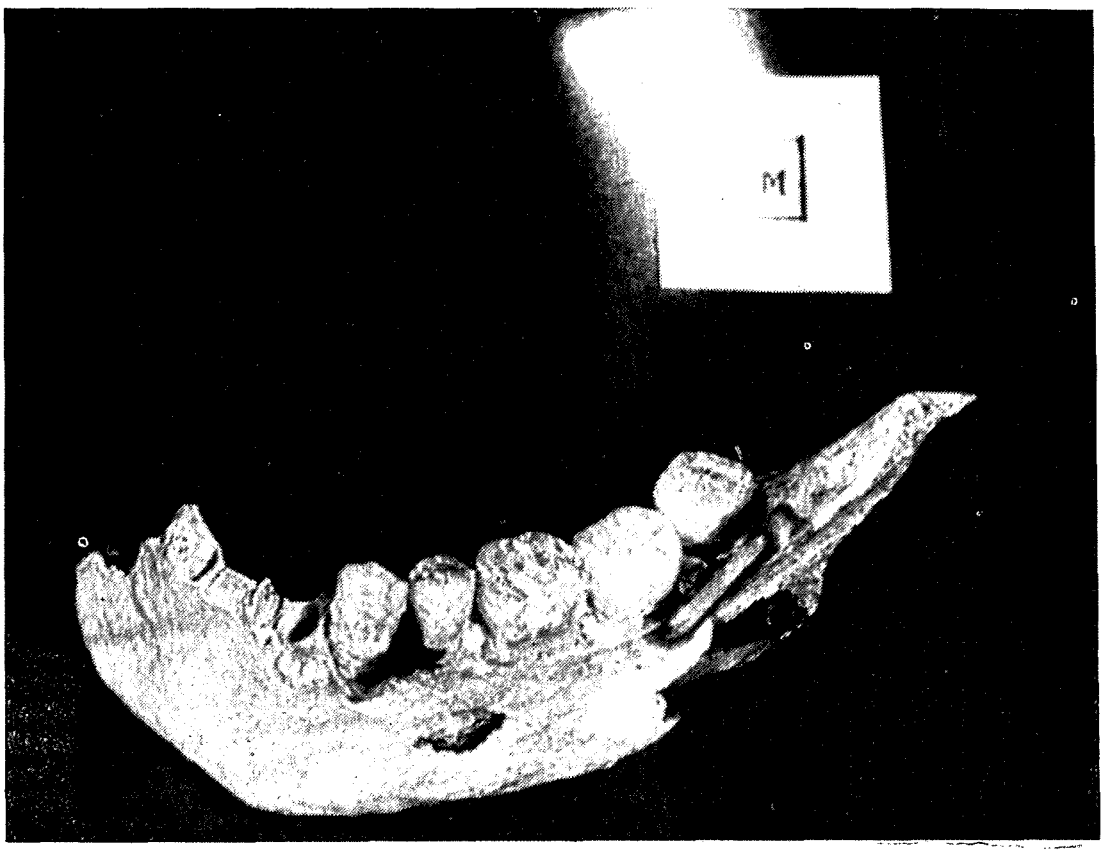
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the body.

Clinical and radiological estimation was made, where possible, of the age, partly according to the eruption and state of teeth and radiographic criteria of McCall and Wald. I believe it was that of an adult person, probably past middle age. The teeth present are fully developed and the fully erupted wisdom tooth shows considerable attrition — a clear proof that it had been used for many years.

The following features were also noted: (a) A well developed fairly broad ascending ramus — ideal for the attachment of a strong masseter muscle. (b) One of the premolars is missing. (c) The five teeth present, canine, premolar and three molars, had been affected by attrition, but are free from any caries. (d) The condition of the teeth is very good indeed, but that of the tooth-bearing bone is weak and crumbling. (e) There are signs of bone destruction in the region of the apex of the premolar (?). (f) Radiographs revealed some deposition of secondary dentine in the pulp chambers. (g) The coarse nature of the diet of our ancestors is demonstrated, in a way, by the attrition of the teeth.

It was estimated by means of modern tests, that the mandible is approximately 1500 years old. It is relevant to mention that according to Sir T. Zammit, "the large number of rock-cut tombs found in different localities in the Maltese Islands prove that for centuries the Maltese buried their dead in graves dug out in the rocks. This custom which probably originated in prehistoric times, continued through the Phoenician, Carthaginian and Roman periods."

RUBELLA

ETHELWALD E. VELLA

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Originally physicians did not and indeed could not make an accurate distinction between the various fever-with-a-rash syndromes such as measles, scarlet fever, typhus and so on, but about 200 years ago various medical papers written by German authors described one such fever-with-rash entity which was most commonly referred to as Rötheln and subsequently became more generally and more popularily known as German measles, precisely because of these geographical and historical antecedents.

Rötheln one must admit is a typical teutonic word, harsh to our unaccustomed ears, requiring good coordination on the part of our tongue, lips and larynx to enunciate; towards the latter half of the last century the army surgeon Veale writing in the Edinburgh Medical Journal (1866) stated 'the attention of the medical profession has occasionally been directed of late years to the occurrence of a peculiar form of eruptive disorder which has certain points of resemblance both to measles and to scarlet fever, and which

would appear to stand nosologically about midway between them. In Germany it has been regarded as a distinct disease and has received the name of Rötheln. The name of a disease is always a matter of some importance. It should be short for the sake of convenience in writing, and euphonious for ease in pronunciation. I therefore venture to propose Rubella as a substitute for Rötheln.'

And so Rubella it has been ever since.

It affected mostly children, it had a certain nuisance importance when it interfered with the parents' social and childrens' educational programmes but no great importance was attributed to it. A laissez-faire attitude prevailed until some time during World War II, (it is of interest to observe that three of the six biggest epidemics so far in this century occurred during World War I, World War II and the Korean War), when from Australia strange hard-to-believe stories about the teratogenic effects of Rubella were being discussed and recorded by, somewhat unexpectedly, eye specialists.

Norman McAlister Gregg (later Sir Norman) was the prime mover in this new field. 'In the first half of the year 1941 an unusual number of cases of congenital cataract made their appearance in Sydney. Their frequency, unusual characteristics and wide distribution warranted closer investigation'. Gregg duly observed and reported cataracts, micro-ophthalmia, nystagmus, retinopathy, corneal clouding; what resounds perhaps even more to his credit he also recorded accompanying patent ductus arteriosus, congestive heart failure, low birth weights, feeding difficulties and even an abnormally high death rate in these unfortunate infants. 'The remarkable similarity of the opacities in the lens, the frequency of an accompanying affection of the heart and the widespread geographical incidence of the cases suggested that there was some common factor in the production of the diseased condition. The question arose whether this factor could have been some disease or infection occurring in the mother during pregnancy which had then interfered with the developing cells of the lens. By a calculation from the date of the birth of the baby it was estimated that the early period of pregnancy corresponded with the period of maximum intensity of the very widespread and severe epidemic in 1940 of German measles'.

Two years later Gregg added: deaf-mutism, dental defect and mental deficiency to abnormalities caused by Rubella. His observations were fully corroborated by many investigators after he had shown the way, though not without the usual scepticisms of doubting Thomases; even "The Lancet" (1944) at one time doubted the correlation of children's malformations with Rubella of pregnant mothers, implying in an Editorial annotation that it was surely very unlikely that such reputedly obvious and serious complications of an infectious fever in pregnancy could have been missed even by the non-medical world.

Still Gregg had the satisfaction before he died in 1966 of seeing his views accepted and his observations confirmed in all countries werever scientific medicine is practised.

The next most significant advance in the history of Rubella, nothing less in fact than the successful isolation of the etiological virus agent itself in the laboratory, circa 1962, is linked with the name of Walter Weller.

Weller and Neva, from the Harvard School, showed that infectious material containing the virus, when inoculated in tissue cell cultures, using cells obtained from the amnion of human placentas, produced visible evidence of the presence of the virus by certain easily detectable morphological changes in the appearance of the infected amnion cells, upon prolonged incubation for 3-5 weeks: 'Viruses apparently not heretofore described, have been isolated from the urine or blood of 4 patients with rubella-like illnesses. These agents were serially propagated in primary human amnion cultures and produced unique cytopathic changes characterised by the aggregation of nuclear material and the presence of inclusion bodies'.

At the same time and working independently a group of workers at the world

(Photo courtesy of the Wellcome Trustees)

Sir Norman McAlister Gregg the Australian ophthalmologist who first showed the teratogenic effects of Rubella in Pregnancy.

famous U.S. Army research establishment, the WRAIR (Walter Reed Army Institute of Research) succeeded in showing that the rubella virus could also invade and infect simian cells obtained from the kidneys of a certain species of monkey — the African Green Monkey. In these infected monkey kidney cell cultures it was not possible to detect a morphological change as compared with the cytopathic effects (CPE) obtained in human amnion cells. Nevertheless there was a biological change, as proof of virus infection could be demonstrated within 7-10 days by the mutual exclusiveness of 2 simultaneous virus infections; thus the rubella-virus infected but visibly unaffected simian cells when subjected to an attempted superinfection by another species of virus were fully refractory to the second invading virus. This is the 'interference' phenomenon, 'During February and March 1961, a new agent was isolated repeatedly from military recruits hospitalised at Fort Dix, N.J. This agent recovered from throat washings has been found to propagate only in a limited number of cell lines. In these it fails to produce cytopathologic effect (CPE). It is recognised only by its ability to interfere with ECHO virus, Type II.'

It is not always easy even in this day and age to diagnose clinically patients suffering from Rubella. There are many diseases which can simulate closely the picture of Rubella, there are many more subclinical infection than frank cases — the "iceberg" phenomenon seen in so many other infectious diseases, and there are

many mildly infected patients who exhibit no rash at all.

The successful isolation of the virus described above not only produced the only truly accurate method of diagnosis by isolation of the causative organism but also provided the means by such viral antigens could be produced in good amounts for the four serological tests used in laboratory diagnosis:

1. HAI — Haemagglutination Inhibition
2. CFT — Complement Fixation
3. Immuno-fluorescence
4. NT — Neutralisation.

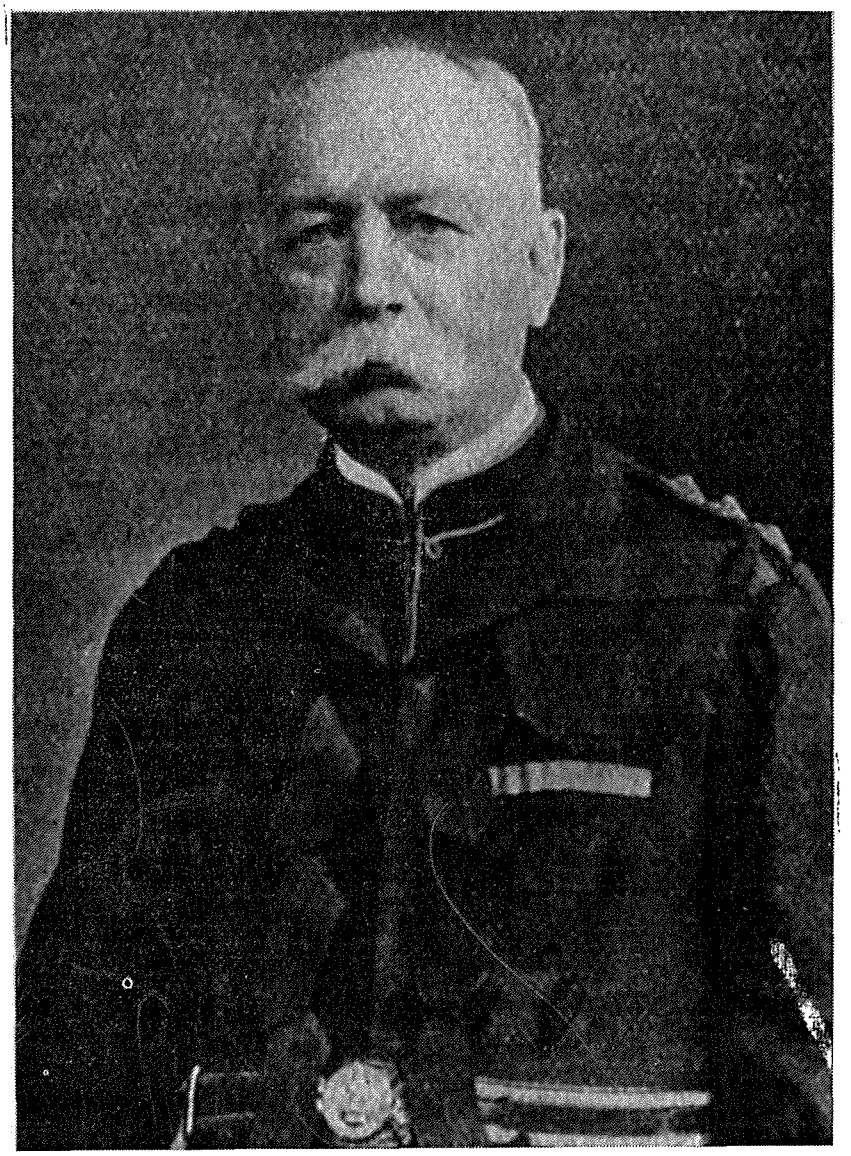
Of these tests the one which is more familiar to most of us and which is in commonest use in most diagnostic laboratories is the HAI; it came into prominence about 3 years ago as the result of the work of Stewart and other investigators of the U.S. Public Health Service, "The haemagglutination inhibition test developed in this laboratory provides a simple, rapid and inexpensive procedure for use in the diagnosis of rubella, in determining status of rubella immunity and in testing the efficacy of experimental rubella-virus vaccines".

In this test the natural property of the rubella virus to agglutinate chicken cells is utilised to detect the presence or absence of anti-rubella antibodies in a patient's serum and thus indirectly to confirm or refute a suspicion of rubella infection. If a patient is infected with the rubella virus his or her serum will contain antibodies which will inhibit this characteristic property of the virus to agglutinate red cells on mixing the three reagents (Rubella virus × Fowl-cells × Patient's serum) together; if the patient is however suffering from some disease other than rubella his serum would possess no specific antibodies against the rubella virus and therefore on mixing the 3 reagents (virus × cells × serum) the uninhibited virus will now actively agglutinate the fowl cell.

This HAI test has proved very useful also in screening individual patients for evidence of past infection, for if a pregnant mother possesses antibodies to rubella (i.e. HAI is positive) as evidence of a past infection with rubella, she can be reassured that no harm will result to her baby as a result of her coming into contact with a case of rubella; conversely in girls and women of child-bearing age the complete absence of antibody represents a real danger that if they get accidentally exposed to rubella when they eventually conceive, they will give birth to a congenitally malformed child, if their child is born at all. For some unknown reason this last observation does not seem to apply as much to Japanese women as to their western sisters.

The second and undoubtedly even more beneficial effect which resulted from the successful culture of the virus was the possibility of manufacturing suitable vaccines. The efforts of research workers in this field were no doubt spurred on by the rubella epidemic of 1963-64 which left thousands of children maimed in its wake and thus provided a great impetus towards the production of an effective prophilactic vaccine to protect susceptible individuals. This has recently become a real possibility at least in well-to-do countries. Present day vaccines contain a live virus which has been however so weakened by artificial culture in the laboratory that it can no longer produce its patholigical effects while nevertheless retaining sufficiently its identity as a foreign agent when injected so that antibodies are produced in the vaccines which are almost as high in titre and possibly as persistent as those which follow natural infection.

For purpose of vaccine production the rubella seed virus is grown in one of four kinds of tissue cells obtained from: Monkey Kidney, Rabbit Kidney, Duck Embryo, Human Embryo, and thus in the relevant literature the reader comes across such hieroglyphics as HPV-77 which stand for a vaccine prepared from a virus which has been weakened by being cultured and subcultured at roughly weekly intervals for 77 times on monkey kidney cells. The first vaccine marketed in the U.S.A. (Merck's) bore the formula HPV-77 DE 5 — meaning that the virulence of the HPV 77 virus was still further attenuated by being serially sub-



The Army Surgeon Henry Richard Lobb Veale who first proposed the name Rubella.

cultured five more times on duck embryo cells. For various reasons duck embryo is a better medium for preparing rubella vaccine than chicken smbryo. Another American vaccine called RA-27/3 and prepared in human fibroblast diploid cells is interesting in that it can be dispensed intranasally by nose drops or spray — a route of vaccinnation which cannot be employed when using the other rubella vaccines all of which have to be inoculated subcutaneously.

The fourth vaccine, and the one which is or will be more familiar to us in Europe is the Belgian vaccine prepared in rabbit kidney (3 passages in Green Monkey Kid-

ney, followed by successive cultures in rabbit kidney for 53 times — GMK 3 — RK 53), it is marketed by Smith, Kline and French and costs about a guinea per dose (0.5 ml).

What of the future? It is fortunate that vaccines have been made available this year; epidemics of Rubella seem to occur every 6 years or so; the last epidemic occurred in many countries during 1963-1965 so that one may expect an epidemic of Rubella in the next 24 months.

Previously human immuno-globulin was our standby in the passive prophylaxis of Rubella but considerable doubt has been cast on its effectiveness; not only was the usual dose of 750 mgm containing an unknown titre of specific rubella antibodies too small but unless the immuno-globulin was given within 24 hours of exposure it could not be really expected to prevent infection. Hence to all intents and purposes we have to rely on "Cendevax" vaccine.

A Rubella vaccination programme that is currently being recommended by the army medical department is as follows:

a) Pregnant mothers are screened for rubella antibodies by adding an HAI test to the usual battery of prenatal serologic tests. If the test proves negative an immediate post-partum vaccination is advised with instruction to the patient to avoid all possibility of conception for the following 2-3 months.

b) Non-pregnant females who request protection are first screened by an HAI test (about 80% of these would be expected to have a positive HAI test and hence would not stand in need of vaccination). If the HAI is negative vaccination is offered with the same precautionary medical advice as detailed in (a) above.

2. Girls between 11-14 years, that is in the prepubertal age and girls approaching school-leaving age who represent the next generation of parents, are offered vaccination without preliminary testing.

In general it may be said that though little or only very mild reactions are to be expected after "Cendevax" vaccines yet rubella vaccines are apt to give more undesirable side effects the older the vaccinee, hence the recommended procedures of giving these female teenagers vaccination without wasting time and money in the preliminary HAI testing which is done in the case of older women of whom 1 in 12 will be found to need vaccination; moreover this single procedure of direct vaccination, as against the two procedures of preliminary HAI testing followed when necessary by vaccination, avoids subjecting the girls to 2 needle jabs which is thought might discourage some of them from accepting vaccination.

It is to be noted that as the situation stands today the pregnant-to-be multipara is the main target needing priority in protection, as she runs the greatest risk of getting infected from her own children with whom she is in daily close contact; at some date in the not so distant future vaccination could with profit be offered to all children of either sex between the ages of 1 to 11 without preliminary HAI screening in an effort to eradicate German measles by mass immunisation on a national scale. It may be also feasible to include Rubella vaccine with other vaccines (Measles, mumps) used for the primary immunisation programme of infants and thus make it more acceptable since this procedure would neither entail an extra visit of the parent and child to a doctor nor require an additional exhibition of syringe and needle.

The duration of protection afforded by Rubella vaccination is not yet known, hence the need for booster doses is not yet excluded.

THE DENTAL NEEDS OF BIRKIRKARA PRIMARY SCHOOL CHILDREN

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Summary

(1) A programme planning survey was performed on 1543 children aged four to thirteen attending Birkirkara Primary School.

(2) An estimate of the prevalence of specific oral diseases and conditions and current needs for treatment has been obtained.

(3) School Dental Health programmes have great usefulness, when based upon dental health education, case finding and preventive procedures. They succeed best when they include good co-operation with medical and school personnel.

Twenty-five years of School Dentistry in these Island have not mitigated the flowing tide of oral disease, nor has there been any remarkable change in the attitude of the community to dental matters.

When the work to be done greatly exceeds his capacity, a dentist can adopt one of two alternatives. He may work at random, placing fillings whenever he can without any particular plan, or he may treat those patients who are responsive and with whom he can form a good relationship, treating them fully and recalling them at regular intervals. Neither is satisfactory. Rather, he must consider the size of the problem, use all preventive measures at his disposal, and create priorities among the younger children to ensure that a block of complete treatment is created and maintained (McKendrick, 1970).

The collection of information concerning community characteristics of a disease is an acknowledged prerequisite to effective planning of a control programme, and if the collection of data is undertaken periodically, an evaluation of the worth of that programme can be made.

A dental survey, consisting of a clinical examination, was performed on 1543 school children, aged four to thirteen years attending the Government Primary School at Birkirkara between the months of February and June, 1970. The objectives of this survey were:

(1) To determine the extent to which existing dental services are coping with the current need for treatment.

(2) To obtain an estimate of the prevalence of specific oral diseases and conditions requiring treatment.

(3) To provide base-line data for subsequent evaluation of dental services and preventive programmes.

(4) To obtain oral health data needed when estimating the cost of maintaining and expanding a dental health programme.

Materials and methods

This survey was carried out during sessions normally devoted to school inspection, and costing, with respect to sample size, was of no consequence. The sample, which was not randomised, included 50% or more persons from each age group, and 61.5% of the total school child population was examined.

All examinations were performed by one clinician and data recorded by one assistant. Instruments and materials used were explorers of the sickle type, plane mouth mirrors, chip syringes, stainless

steel sterilising pans, and a 75 watt light source in an angle-poise lamp. The use of radiographs was considered impracticable.

Dental caries

Standards of assessment (W.H.O. 1962 and 1965)

A tooth is considered present when visible or detectable with an explorer. When a deciduous tooth and its successor both occupy the same tooth space only the permanent tooth is counted. Observations were recorded for the whole mouth in order that a correct assessment of caries-free individuals could be made.

Decayed teeth

Dental caries is considered present when the lesion has a softened floor or wall, or undermined enamel. These criteria apply to the one-surface interproximal lesion which can be explored directly; when an adjoining tooth is present, the criterion of diagnosis is a collapsed marginal ridge. White or chalky spots, discoloured or rough spots, and hard, stained pits or fissures which just catch on the explorer point are not recorded as caries. When a tooth has one or more filled surfaces, and another surface which is carious, or there is recurrent caries around a filling, or the tooth contains a temporary restoration, the tooth is scored as decayed (d) or (D). A decayed deciduous tooth which is about to be exfoliated, but no part of its successor is detectable in the mouth, should also be classed as (d).

Missing teeth

A permanent tooth is counted as missing (M) only when it has been extracted primarily because of caries. No measure of missing teeth is made for the deciduous dentition.

Teeth indicated for extraction

A tooth is classed (i) or (I) when caries has so destroyed the crown that it may not be restored. Included in this category are teeth where decay has involved four or more surfaces and residual roots.

Filled teeth

Teeth are considered filled, (f) or (F), whenever a filling of any permanent material is present, and there is no recurrent decay.

Indices of caries experience

Summarisation is made separately for the sexes and for the deciduous and permanent dentitions.

The report includes per cent. persons with caries, and age-specific, d.f. and D.M.F. per person. Separate figures are given for (d) or (D), (i) or (I), (f) or (F), and (M). These are measures of intensity, indicating the average number of teeth affected per person. A measure of scatter around the mean is afforded by the standard deviation computed for each age group and the sexes separately.

To assess treatment needs in greater detail, data are made available on:

Mean decayed surfaces per person.

Point prevalence rates. These indicate per cent. population with one or more cavities (d) or (D), with one or more teeth indicated for extraction (i) or (I), with one or more teeth missing because of caries (M), or with one or more teeth filled (f) or (F).

Measures of incidence. When age-specific d.f. and D.M.F. rates are available it is possible to estimate the incidence of clinical caries between any two ages, by subtracting the number of d.f./D.M.F. teeth per person at the younger age from the number of d.f./D.M.F. teeth at the higher age. Reckonings for the deciduous dentition are attempted only for children under 6 years, as calculations are complicated by the natural shedding of primary teeth in older children.

Periodontal disease

Standards of assessment (W.H.O. 1962 and 1965)

A rapid examination of the whole mouth is conducted with mirror only. Periodontal status is measured in terms of the condition of the periodontal tissues. In

order to assess local factors related to this condition the presence of calculus was recorded and the amount of soft debris covering the teeth was also graded. The gingivae around all teeth present, except residual roots, are considered in making this assessment. Sites of dental abscess or sinus, and areas of inflammation secondary to food impaction in open interproximal cavities are ignored. One recording is made for the whole mouth based on the most severe condition observed. The classification of periodontal status was completed in under one minute.

Periodontal status

Criteria

Good — Absence of intense gingivitis and destructive periodontal disease

At *first* glance no conspicuous change in colour of the gingival tissues is noted and there is no periodontal pocket. Persons having minor alterations in gingival form alone without definite colour change or bleeding on digital palpation are included in this category.

Fair — Presence of intense gingivitis

At *first* glance, one or more gingival areas are found to have marked changes in colour to a definite red or bluish-red and/or there is bleeding on digital palpation.

Poor — Presence of destructive periodontal disease

This condition is considered present when there is a periodontal pocket resulting from loss of bone accompanied by gingival inflammation. Alveolar resorption accompanied by gingival recession and exposure of cementum is considered as destructive periodontal disease only when accompanied by intense gingivitis.

Note: Periodontal status is scored "Fair" or "Poor" only when no doubt exists that the criteria for the particular condition have been met.

Calculus

Calculus is considered present only when deposits can be seen on one or more teeth by inspecting all exposed tooth surfaces with the aid of a plane mirror, i.e. only obvious calculus is scored. An explorer is used only to confirm that a deposit which is visible without probing is in fact calcified.

Periodontal disease and calculus data are reported as per cent. of persons:

(1) with intense gingivitis only
(2) with destructive periodontal disease
(3) with obvious calculus.

Oral debris

Limited information on the status of oral cleanliness is obtained by inspecting the labial surfaces of upper and lower anterior teeth. The tine of an explorer is run on the surfaces of the teeth concerned to determine the presence and extent of plaque and materia alba.

One recording of the highest score is made for the whole area inspected. Oral debris and extrinsic stain (green only) are scored together:

0: no debris or extrinsic stain
1: soft debris covering not more than one third of any tooth surface or the presence of extrinsic stain without debris regardless of the surface area covered
2: soft debris covering more than one third of any tooth surface.

Traumatic injuries to anterior teeth

Criteria for assessment

Missing, displaced or loose teeth, and darkening of the clinical crowns are not recorded. Only upper and lower permanent incisor teeth with part or parts of their crowns deficient are scored. Data recorded as per cent. persons affected and mean number of fractured teeth per person so affected.

Results

Dental Caries

The age range for the school population and the numbers and percentages of children inspected are shown in *Table 1.*

Table 1
Government Primary School, Birkirkara.
Age range as on 30th. September, 1969

Age last birth-day	Male	Female	Number inspected			
			Male	percent	Female	percent
4			7		13	
5	190	181	94	49.5	97	53.6
6	148	134	83	56.1	73	54.9
7	206	199	113	55.0	110	55.3
8	163	160	91	55.8	99	61.9
9	155	194	83	53.5	119	61.3
10	131	141	86	65.7	102	72.3
11	137	94	104	76.0	63	67.0
12	101	55	71	70.3	39	70.9
13	50	69	44	88.0	52	
Total	1281	1227	776		767	

The Deciduous dentition

Table II shows percentage of persons affected and age specific mean d.f. rates. Separate data are presented for (d), (i), (f) and for the sexes. Data on d.f. (S) are shown in *Table IV. Figure I* gives the point prevalence rates for the deciduous dentition. The d.f. rates for both sexes are similar but, once decayed, girls' teeth appear to deteriorate and are lost at a faster rate than boys'.

The four-year-old group was too small to draw broad conclusions from, but 51.6% had one or more decayed teeth, twenty children requiring forty fillings between them.

The d.f. rate rises through age six years and then falls to nil after the thirteen years as the deciduous teeth are shed.

If the primary teeth indicated for filling in the four to eight year old group were restored, and other teeth for this and the remaining group extracted, it would be necessary to place 1,525 restorations and to perform 930 extractions. If five and six year old children were to receive priority, it would be necessary to place 765 fillings and to extract 125 teeth for 390 and 70 children respectively. An annual increment of 0.15 d.f. teeth and 0.40 d(S) is to be expected at age 6 years.

Table IV Dental Caries

Decayed Surfaces

MALE AGE	Number Examined	Per Person Mean df (S)	Per Person Mean DMF (S)	FEMALE AGE	Number Examined	Per Person Mean df (S)	Per Person Mean DMF (S)
5	94	2.2	0.02	5	97	2.5	0.15
6	83	2.6	0.05	6	73	2.8	0.16
7	113	2.7	0.09	7	110	3.1	0.23
8	91	3.3	0.44	8	99	3.4	0.68
9	83	2.3	0.54	9	119	1.9	0.73
10	86	1.3	0.62	10	102	1.8	1.2
11	104	1.0	1.0	11	63	0.4	1.1
12	71	0.27	1.2	12	39	0.15	1.3
13	44	0.13	1.3	13	52	0.42	1.0

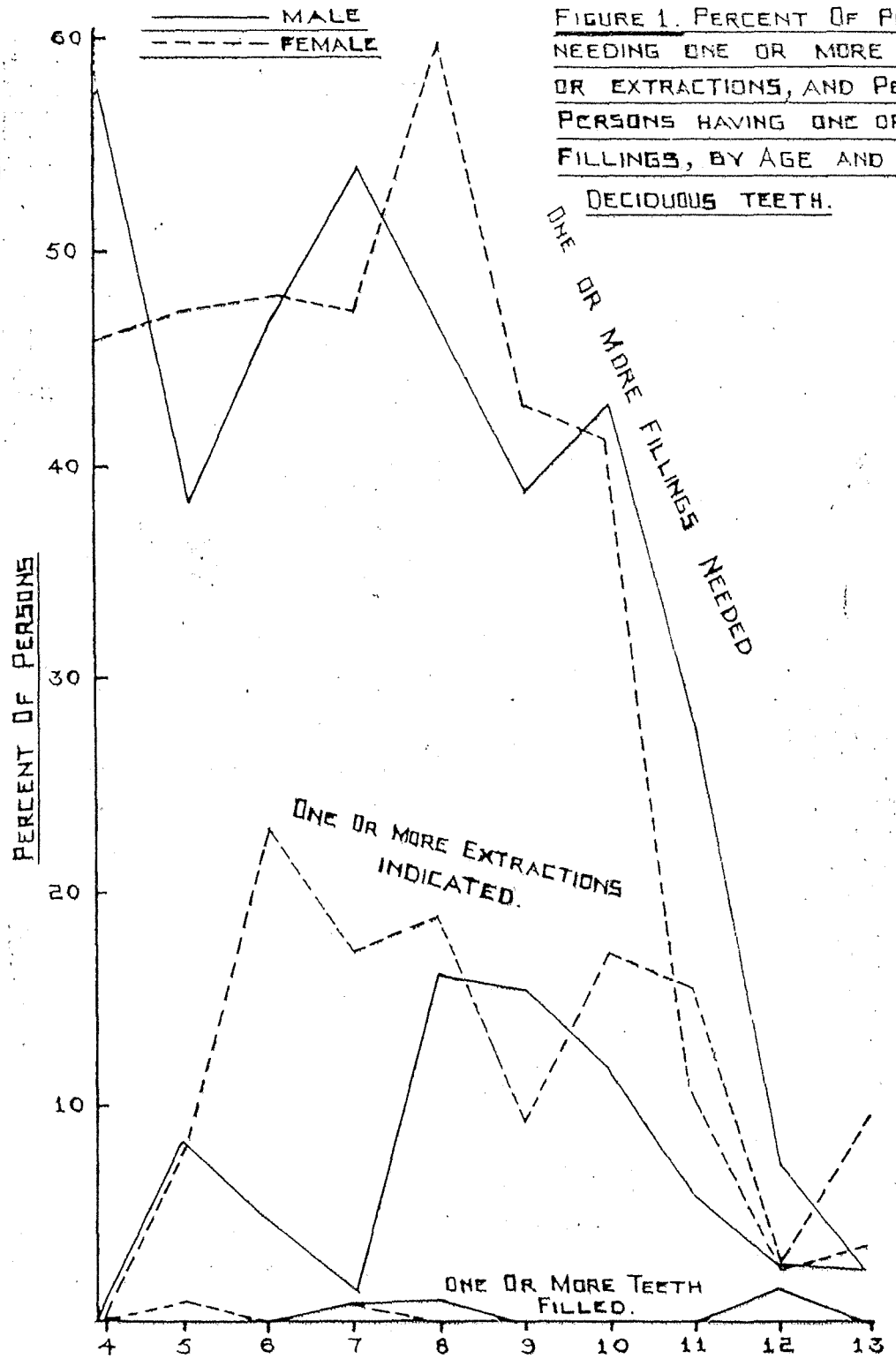

FIGURE 1. PERCENT OF PERSONS NEEDING ONE OR MORE FILLINGS OR EXTRACTIONS, AND PERCENT PERSONS HAVING ONE OR MORE FILLINGS, BY AGE AND SEX.

DECIDUOUS TEETH.

Table II Dental Caries
Incidence in deciduous teeth

MALE Age	Number Examined	Number Affected (percent)	Per Person d	f	i	df	Standard Deviation
4	7	57.1	2.57			2.57	0.876
5	94	40.4	0.96		0.18	1.14	1.193
6	83	47.0	1.40		0.08	1.48	1.881
7	113	59.3	1.00	0.02	0.24	1.26	1.454
8	91	53.8	0.91	0.03	0.25	1.19	0.447
9	83	42.2	0.70		0.25	0.95	1.343
10	86	47.7	0.66		0.14	0.80	0.604
11	104	39.4	0.39		0.09	0.48	0.823
12	71	8.5	0.07	0.03	0.03	0.13	0.146
13	44	4.5	0.02		0.02	0.04	0.235
FEMALE Age							
4	13	46.2	1.38			1.38	1.688
5	97	47.4	1.20	0.01	0.16	1.37	1.286
6	73	53.4	1.07		0.25	1.32	1.594
7	110	50.9	1.04	0.01	0.30	1.35	1.880
8	99	63.0	1.33		0.28	1.61	1.912
9	119	47.9	0.70		0.16	0.86	1.148
10	102	45.1	0.54		0.20	0.74	1.012
11	63	14.0	0.21		0.02	0.23	0.497
12	39	5.0	0.03		0.03	0.06	0.217
13	52	11.5	0.13		0.04	0.17	0.552

The mean d.f. rate for both sexes tends to fall after age six years, however there is a further rise for girls at age eight. An average increment of 0.3 d(S) per year can be expected for ages seven and eight.

The extent of the area devoted to "d" and "i" compared to "f" in *Figure 1* indicates neglected needs and low demands for dental care. Treatment indices have been devised in an attempt to indicate the amount of dental treatment received by a group. The Jackson Index (Jackson, 1961) for filled deciduous teeth in six, seven and eight year olds is nil %, 0.8% and 0.7% respectively.

The Permanent Dentition

Table III shows age-specific D.M.F. rates with separate data for (D), (M), (I) or (F), and the sexes. 7.7% of four year old girls included in this study have already acquired one or more permanent teeth.

Figures II A and *B* depict age-specific point prevalence rates for the permanent dentition.

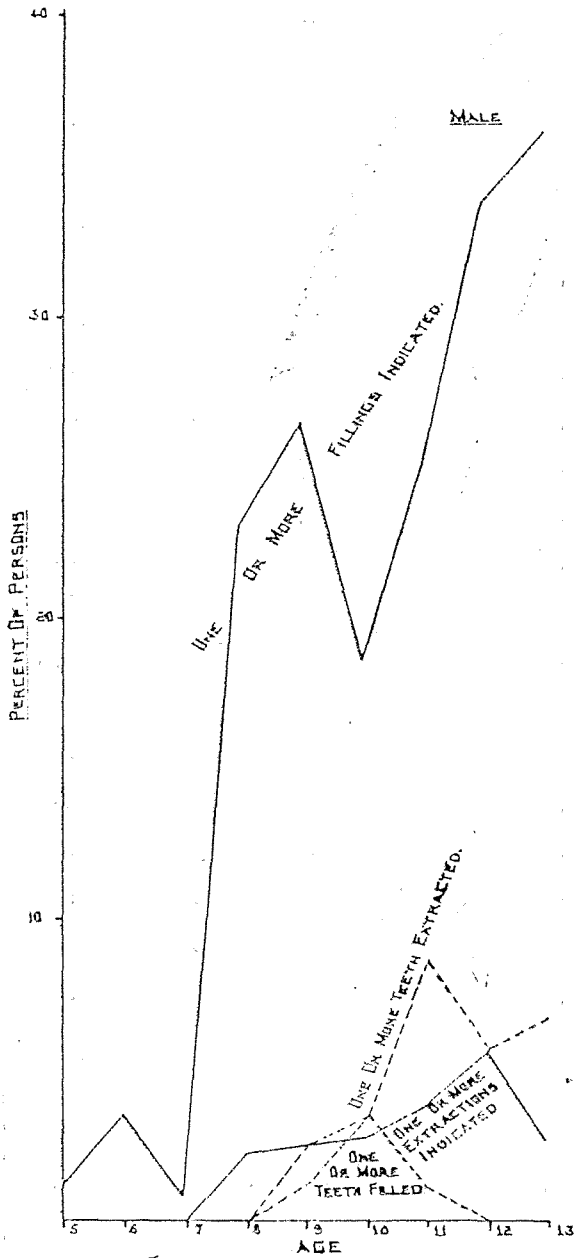

FIGURE II A PERCENT PERSONS NEEDING ONE OR MORE FILLINGS OR EXTRACTIONS, AND PERCENT PERSONS HAVING ONE OR MORE FILLINGS OR EXTRACTED TEETH, BY AGE PERMANENT TEETH.

The D.M.F. rates for both sexes are very low up to the age of seven years, but later rise abruptly and then continuously. Girls are affected more than boys, but they also tend to acquire their permanent teeth earlier.

If priority groups were recognised at ages five and six it would be necessary to treat 40 persons and to place 60 restorations. The requirements of the entire school population are 700 restorations and 60 extractions.

Table III Dental Caries

Incidence in Permanent Teeth

MALE Age	Number Examined	Number Affected (percent)	Per Person D	F	I	E	DMF	Standard Deviation
5	94	1.1	0.02				0.02	0.205
6	83	3.6	0.05				0.05	0.191
7	113	7.0	0.09				0.09	0.341
8	91	23.1	0.35		0.02		0.37	0.723
9	83	30.0	0.34	0.02	0.02	0.02	0.40	0.677
10	86	25.6	0.24	0.05	0.05	0.03	0.37	0.615
11	104	31.7	0.40	0.04	0.05	0.12	0.61	1.026
12	71	41.0	0.53		0.08	0.07	0.68	0.990
13	44	36.4	0.73		0.05	0.09	0.87	1.358
FEMALE Age								
5	97	8.2	0.15				0.15	0.562
6	73	11.0	0.17				0.17	0.524
7	110	13.7	0.19			0.01	0.20	0.738
8	99	31.0	0.42	0.02	0.04	0.02	0.50	0.914
9	119	26.0	0.35		0.02	0.06	0.43	0.597
10	102	32.4	0.53	0.08	0.04	0.11	0.76	1.104
11	63	36.5	0.35	0.13	0.01	0.14	0.63	1.012
12	39	41.0	0.59	0.20	0.05	0.08	0.92	1.649
13	52	40.4	0.73	0.06	0.02	0.02	0.83	1.222

An annual increment of 0.03 D.M.F. teeth is to be expected at six and seven years, and, on average, 0.1 D.M.F. teeth per year thereafter. A D(S) increment of 0.06 is expected at seven, years, 0.4 for the eighth year, and, on average, 0.2 D(S) per year thereafter.

The distribution of affected first permanent molars was computed for the group as a whole and for the sexes and the two jaws.

The age-specific distribution of carious or filled surfaces was also worked out as a percentage of the surfaces of the teeth so affected It was assumed that all teeth with fillings have at some time been carious.

Mandibular first molars decay more rapidly than their opposite counterparts, more so in girls than in boys, the attack in girls reaching its greatest intensity at ten years. The attack on girls' maxillary first molars tends to reach its peak at ten years, whilst the rate of decay of maxillary first molars in boys continues to rise through thirteen years of age.

Not only the average number of permanent teeth affected by caries but also

FIGURE IIB. PERCENT PERSONS NEEDING ONE OR MORE FILLINGS OR EXTRACTIONS, AND PERCENT PERSONS HAVING ONE OR MORE FILLINGS OR EXTRACTED TEETH, BY AGE. PERMANENT TEETH.

the percentage of persons who have experienced attack on the permanent teeth also increases with age.

The D.M.F. rate although remaining very low throughout starts to rise more steeply at seven years of age reaching its peak intensity (0.85) at thirteen years of age for all groups. From age five to age twelve girls have higher age-specific D.M.F. rates than boys.

It is the rate of decay of first permanent molars that accounts for the rising D.M.F. rate, and the great majority of cavities occur on readily accessible surfaces. A residual operculum may be important environmental factor in the etiology of distal lesions in mandibular first permanent molars. The data recorded may be an underestimation of the prevalence of interproximal lesions as radiographs were not available during this study.

In *Figures II A* and *B*, the areas representing "D" and "I" compared to "E" and "F" (which are a measure of persons who have received treatment) again depict unmet needs and a low demand for dental care.

Jackson's Index for filled permanent teeth reaches a peak figure of 12.5% at age twelve, this figure being mainly contributed to by the female group. The highest recording for extracted teeth is found at age eleven with a score of 21%, both sexes making almost equal contributions to this figure.

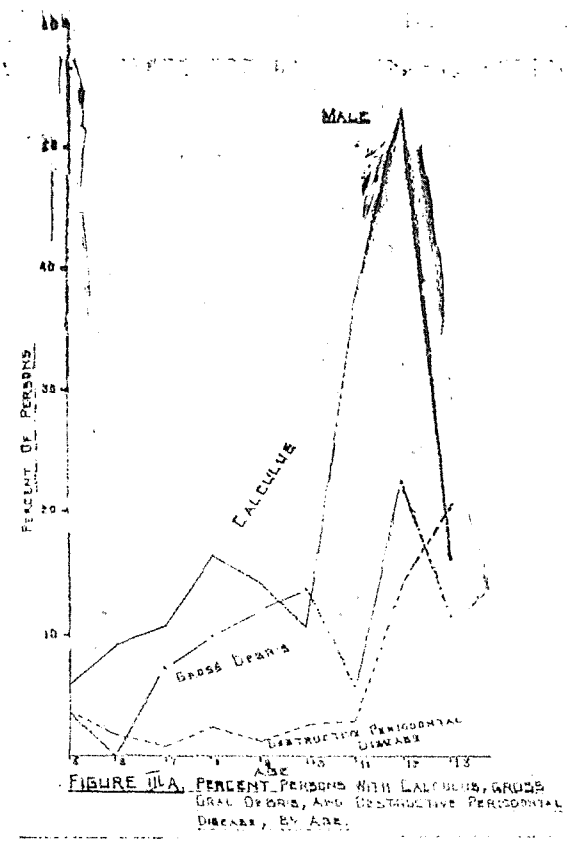

FIGURE III A. PERCENT PERSONS WITH CALCULUS, GROSS ORAL DEBRIS, AND DESTRUCTIVE PERIODONTAL DISEASE, BY AGE.

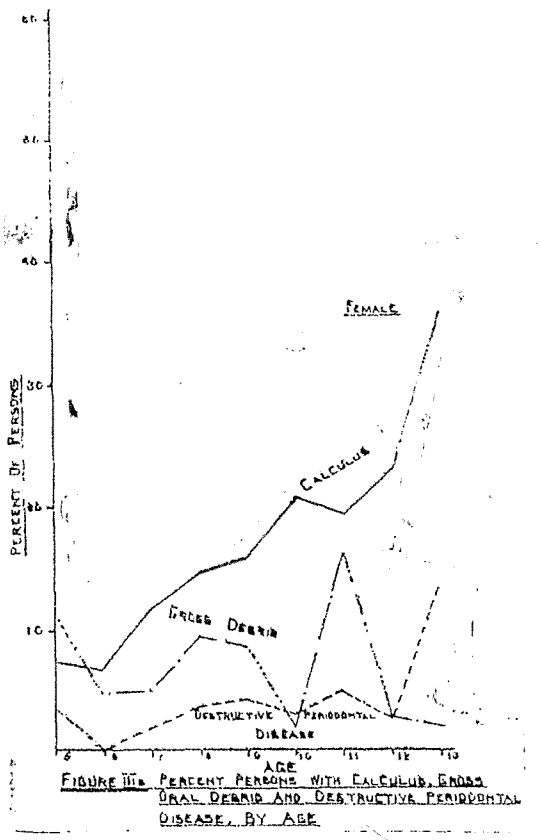

FIGURE III B. PERCENT PERSONS WITH CALCULUS, GROSS ORAL DEBRIS AND DESTRUCTIVE PERIODONTAL DISEASE, BY AGE.

Periodontal Disease

The percentages of girls and boys affected with intense gingivitis (Fair) and destructive periodontal disease (Poor) are shown in *Table V*. An assessment of local factors related to the causation of periodontal disease is afforded by data in *Figures III A* and *B*.

The per cent. population with intense gingivitis is low at age six, but rises steeply as the deciduous incisors are replaced by their successors. This rise achieves its peak at age eight in girls annd age nine in boys. Through eleven years the incidence of intense gingivitis among girls diminishes rapidly but that for boys again rises steeply so that at age thirteen 65.9% are affected.

The prevalence of destructive periodontal disease among girls rises gradually from age six to age twelve so that at thirteen years 13.5% are affected. The prevalence rate for boys which had until eleven years followed that for girls but

Table V Periodontal Disease

MALE Age	PERIODONTAL STATUS percent Affected		CALCULUS	ORAL DEBRIS			Number
	Fair	Poor	(Present percent)	0	1	2	Examined
5	16.7	3.7	5.5	37.8	58.4	3.8	55
6	5.4	1.8	9.1	53.6	46.4		56
7	25.9	0.9	10.7	26.8	66.1	7.1	112
8	37.4	2.2	16.5	18.7	71.4	9.9	91
9	53.0	1.2	14.5	13.3	74.7	12.0	83
10	41.9	2.3	10.5	14.0	72.1	13.9	86
11	50.0	2.9	37.5	12.5	81.7	5.8	104
12	50.7	14.1	53.5	14.1	63.4	22.5	71
13	65.9	20.5	15.9	11.4	54.5	34.1	44
FEMALE Age							
5	17.9	3.6	7.2	41.8	47.3	10.9	55
6	8.1		6.5	55.0	40.3	4.7	62
7	29.1	1.9	11.7	30.1	65.0	4.9	103
8	50.5	3.3	14.3	28.2	62.6	9.2	99
9	41.1	4.1	15.9	20.2	71.4	8.4	119
10	46.5	2.9	20.8	25.8	72.3	1.9	101
11	46.8	4.9	19.4	16.5	77.4	16.1	62
12	38.0	2.6	23.1	31.8	66.6	2.6	39
13	27.0	13.5	36.5	23.0	75.0	2.0	52

at a lower level, rises steeply and continuously beyond that age so that at thirteen 20.5% of boys are affected.

The graphs depicting the prevalence of destructive periodontal disease, obvious calculus and gross debris *(Figures II A* and *B)* in both sexes are similar. There is a sharp rise in the number of children with calculus through the age of ten so that the percentage of twelve year olds affected is 53.5 and 36.5 for boys and girls respectively.

More than half the number of girls and boys examined had clean mouths at age of six, but, at age thirteen, this figure drops to 11.4 and 23.0 for boys and girls respectively. The percentage of boys with poor oral cleansing increases with age and more rapidly through age eleven. The percentage of girls with gross debris diminishes with age then rises abruptly to a peak at age eleven.

Fractured Incisors

Up to the age of nine years girls tend to incur more injuries to their anterior teeth than do boys, a tendency to bilateral involvement being especially marked at age seven. There is a very sharp increase in the percentage of persons affected at age ten. Through this age the per-

Table VI Fractured Incisors

Male Age	Number Examined	Persons Affected percent	Mean number of Fractured teeth per Person so affected
7	113	0.9	1.0
8	91	2.2	1.0
9	83	4.8	1.0
10	86	17.5	1.4
11	94	15.9	1.1
12	71	7.0	1.4
13	44	18.1	1.4
Female Age			
7	108	0.9	2.0
8	99	4.0	1.2
9	119	8.4	1.1
10	102	15.7	1.2
11	63	6.3	1.2
12	39	2.6	1.0
13	52	5.8	1.3

centage of boys affected remains high so that at thirteen 18.1% have sustained injuries to their anterior teeth resulting in the loss of tooth substance.

The prevalence for all ages examined is 9.5% and 6.2% in boys and girls respectively, with a greater tendency for multiple involvement in girls.

Conclusion

The caries experience of Maltese primary school children has been described as "encouragingly low" (Mangion and Olivieri Munroe, 1968). Indices of intensity computed for Birkirkara primary school children are even lower. However, other data considered, two children out of five have decayed primary teeth, yet only one in every four hundred have received conservative treatment; one in four have carious permanent teeth, yet only one in eighty of those affected have fillings.

Neglect on this scale is especially costly in the case of dental disease, because of its cumulative nature and the nature of the treatment required. Once under way, dental caries can rarely be checked except by the application of relatively time-consuming procedures. This tremendous backlog of need is of major importance for purposes of programme-planning, and must be clearly distinguished from the new needs which are constantly developing.

An important goal of public health dentistry is to clear up accrued needs at an early age so that subsequent maintenance on a periodic recall basis can prevent any large accumulation of incident needs. Such programmes might also help establish habits of seeking dental care regularly which would carry over into adult life.

A strong correlation has been observed between the prevalence and severity of periodontal disease and the accumulation of calculus and plaque. This view has been expressed by other workers (Waerhaug, 1967, Olivieri Munroe, 1968).

The management of periodontal disease should be based on prevention rather than on cure. A series of clinical trials have demonstrated that gingivitis and tooth mobility can be drastically reduced by improving oral hygiene (Alexander, Morganstein and Ribbons, 1969, Waerhaug, 1967, and Lindhe and Wicen, 1969).

A child must learn proper dental health habits during the early years. During the first three years of life it is the family doctor and the health visitor who is in more frequent contact with the family as a unit. It is the duty of the dental profession to see that these professional colleagues are properly equipped to impart accurate, practical, common sense knowledge.

We must provide school teachers with good, clear, well-designed visual aid material for specific age groups, whether it be films, film strips, posters, leaflets, wall charts ,or teachers' notes from which they can develop their own projects with minimum effort (Davis, 1967).

Acknowledgements

I am indebted to the Headmaster, Headmistress, and Teachers of Birkirkara Primary School who contributed to the smooth progression of the inspections. I am also grateful to Miss C. Agius, School Dental Nurse, for her clerical assistance throughout this survey.

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JOINT LIMITS FOR SYSTOLIC AND DIASTOLIC BLOOD PRESSURE READINGS

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Summary

In the construction of normal limits for a set of variables allowance must be made for the intercorrelation among them. A method of doing this is presented based upon the multivariate normal distribution. It is illustrated for the systolic and diastolic blood pressure readings on a selected group of outpatients. The way in which this approach can be utilized in the clasification of patients into different disease states is also discussed.

Biochemical and physical measurements are generally considered individually in clinical medicine. Often they are compared with similar measurements taken on a group of supposedly healthy subjects, for which 95% normal limits have been set up by adding to and subtracting from the mean twice the standard deviation. If a measured reading on a patient lies within these limits it is felt that as far as that variable is concerned the patient under study is not different from the normal group. Such limits suppose, of course, statistically "normal" distribution for the variables and adequate samples from which to calculate the means and the standard deviations. To overcome these limitations the percentile technique is sometimes recommended since this method does not make any assumption about the form of the distribution (Herrera 1958).

In some cases it may be worthwhile to look at measurements of different characteristics on the same patient simultaneously, taking into account their interrelationship. In the following note a method of doing this will be illustrated for blood pressure readings. It was originally investigated for the analysis of

biochemical measurements, though such measurements are on the whole so poorly correlated that probably little advantage is to be gained by considering them in this way. However the intercorrelations among selected sets of biochemical determinations may be large enough to make the following treatment useful.

Presentation of Blood Pressure Readings

Systolic and diastolic blood pressure readings are usually presented together. Their normal limits are customarily stated as 120 ± 30 mm. of Hg. for the systolic, and 80 ± 20 mm. of Hg. for the diastolic, and can be represented on a linear scale as two separate intervals. As estimates of closely associated functions, these measurements are definitely correlated. Attempts are sometimes made to take this association into consideration by combining them into an index, as for example, in the pulse pressure or the mean arterial pressure.

The two blood pressure readings can be examined jointly, by plotting them as points in a plane defined by two rectangular axes, one axis standing for the systolic scale and the other axis for the diastolic scale, as illustrated in Figure 1. The resulting swarm of points forms an ellipse with tilted axis; the higher the correlation between such variables the greater the departure of the ellipse from the circular form. A curve can then be drawn superimposed on the scatter diagram to include, say 95% of the points within its confines, and in this way define a region of points which may be considered typical of the group. The points outside this region can be interpreted as extreme or atypical values. This will result in misclassifying 5% of normal individuals as abnormal.

These ellipses can be readily drawn if it is possible to assume a normal bivariate distribution of the blood pressure readings. A computer program has been developed for this purpose. It will calculate the means and standard deviations of the two variables, together with the correlation coefficient, and using these will then draw curves to include any given percentage. The curves are called centour ellipses of equal frequency (Rulon *et al.* 1965, Cooley *et al.* 1962), the term centour being derived from the words percentile and contour. It indicates the proportion of individuals with blood pressure readings which occur less frequently than the one considered, and in this sense more atypical. The point specified by the two means, i.e. the centroid, is then the 100 centour. Only 5% of cases will fall outside a centour of 5 and these can then be considered as not belonging to the normal group.

A table of centour equivalents can also be constructed. The table is entered with readings for the two variables and the centour scores read.

Out-Patient Study

To illustrate the above ideas a group of 314 patients were sifted from a study done on about 1000 out-patients at the Toronto General Hospital (Young *et al.*, 1965). Only those patients were chosen who were found after extensive physical examination and laboratory tests, to be suffering from no major systemic illnesses. From this group 196 patients between the ages of 15 and 44 years were selected since there was no substantial increase of blood pressure with age over this interval. The resulting patients were thought to represent "healthy" out-patients.

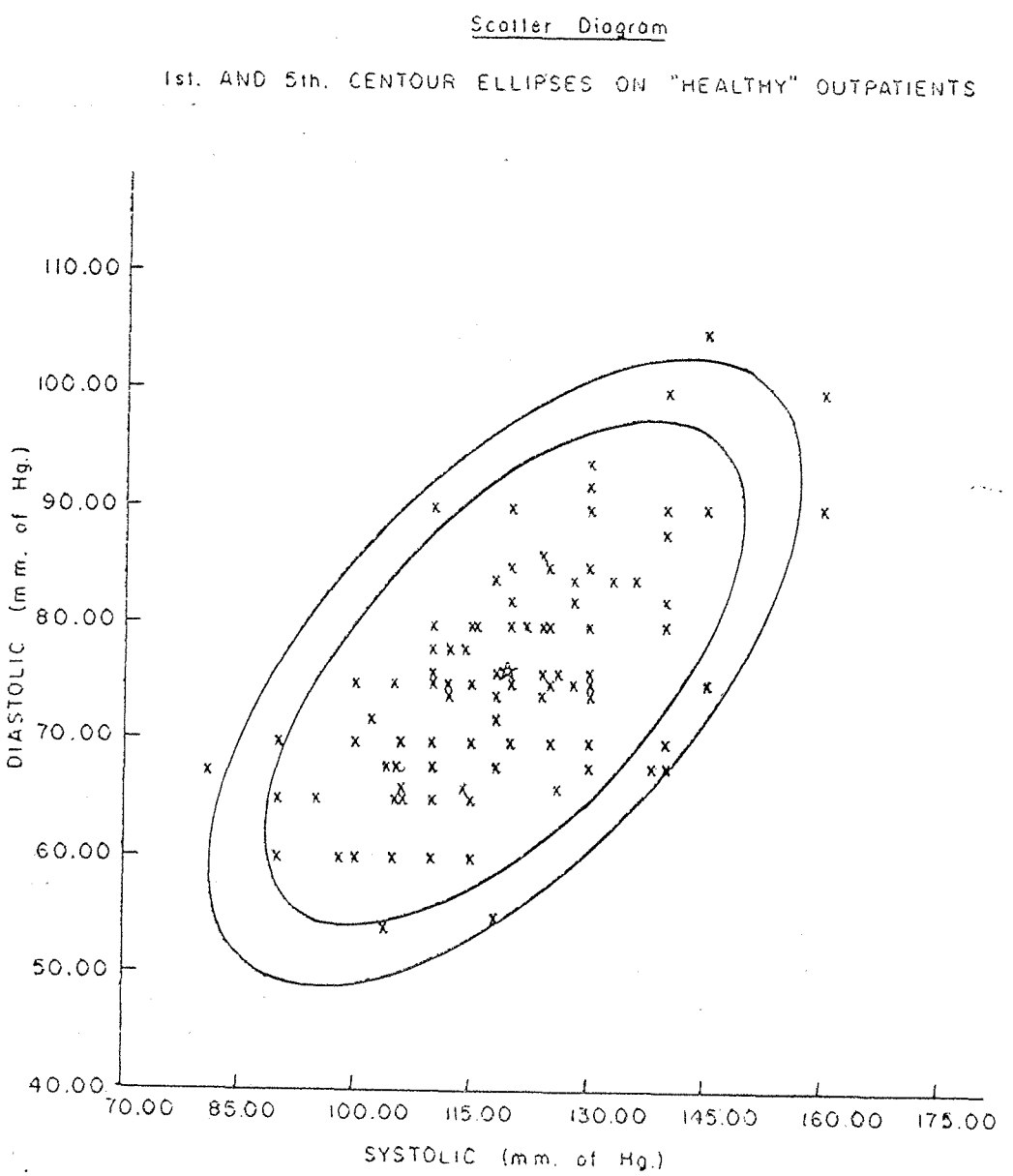
From the blood pressure values of this group, the basic statistical quantities were calculated (Table 1). The data were

Table 1

Summary of Blood Pressure Readings on 196 "Healthy" Out-Patients

(Age, 15 to 44 years)

	Blood Pressure (mm. of Hg.)	
	Systolic	Diastolic
Mean	119.8	76.0
Standard deviation	13.9	9.2
Correlation coefficient	+ 0.59	



then plotted, together with the 1st and 5th centours, as shown in Figure 1. An estimated 1% of cases fell outside the 1st centour and 5% outside the second. Three aberrant values were omitted from the figure, as the main purpose of this note is to illustrate this method and not to supply standards of reference.

A table of centour equivalents was also constructed from the above data, for more convenient use (Table 2). From it, for example, an individual with a blood pressure of 135/85 can be seen to lie on the 42nd centour. Similarly, an individual with a blood pressure of 135/65 can be seen to lie on the 1st centour ellipse, outside of which only 1% of blood pressure values occur. In this case the individual is unusual, though both blood pressure readings lie within normal limits. If based

TABLE 2

Centour Equivalents of Blood Pressure Reading on "Healthy" Outpatients (Age 15 to 44 years)

SYSTOLIC (mm. of Hg.)	DIASTOLIC (mm. of Hg)												
	45	50	55	60	65	70	75	80	85	90	95	100	105
80													
85			1	2	1								
90		1	3	6	6	3	1						
95		1	5	11	15	12	5	1					
100		1	6	17	29	28	16	5	1				
105			5	20	42	53	38	17	4				
110			4	18	47	74	69	38	12	2			
115			2	12	40	80	93	65	27	6			
120				6	26	66	98	86	44	13	2		
125				2	13	42	78	87	57	22	5		
130					5	20	48	67	56	27	8	1	
135					1	7	22	40	42	26	9	2	
140						2	8	18	24	19	9	2	
145							2	6	10	10	6	2	
150								1	3	4	3	1	
155										1	1		
160													

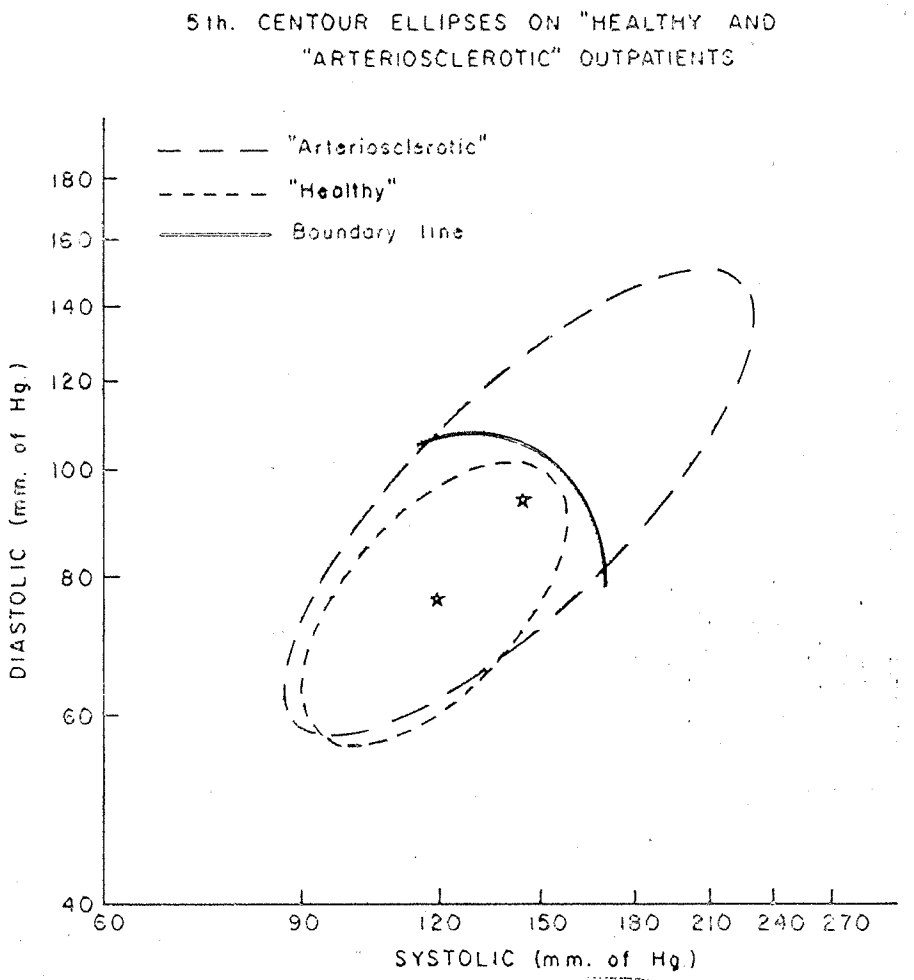
on more substantial data such diagrams or tables could be used in an out-patient setting as an aid in evaluating blood pressure readings on patients.

Several Groups — Problem of Classification

Centour ellipses can also be constructed for data collected from any group of patients suffering from a particular disease, for comparison with the standard healthy group. If a patient is suspected of belonging to this group, comparison of the centours — normal and sick — will suggest in which group the individual belongs, provided that the two groups are sufficiently far apart that the overlap between the ellipses is not too great. Such comparison should allow, if possible, for the relative frequency with which the two types generally occur. If this can be meaningfully specified, then a curve can be drawn which separates the plane into a region where values would be taken as belonging to the other. The best boundary line is the one which gives the least number of misclassifications. It will pass through the points of intersection of equivalent centour ellipses selected so that the frequency of occurrence of individuals on the adjusted contour lines is the same in the two groups.

To illustrate these points, a further group of patients who were suffering from a number of cardiovascular conditions was isolated from the out-patient data. An effort was made to keep the group as uniform as possible by excluding cases with other non-vascular disease. For comparisons with the previous group of "healthy" out-patients, those patients in the same age bracket, i.e. 15 to 44 years, were selected. There were only 17 patients in this group, obviously too small a size for making worthwhile inferences. However it can be used to illustrate this extension of the general idea.

The resulting 5% centour ellipse for the "arteriosclerotic" group is shown in Figure 2 along with the equivalent ellipse for the "healthy" group. A logarithmic



scale has been used since the distribution of the readings for the "arteriosclerotic" group tends to be asymmetrical. Even though the centour for the "arteriosclerotic" group is poorly determined, it is clear that there is so much overlap between the ellipses that classification obviously cannot be made with confidence using only this information. The relative frequency of the two types, 196:17, can however be added to establish a boundary line between the "healthy" and the "arteriosclerotic" groups (Figure 2). It passes through the points of intersection of those centours for which individuals in the two groups are estimated to occur with equal frequency in the out-patient population. Any values lying on one side of the boundary line can now be classified as normals and those on the other side as abnormals. This would result in minimal misclassification. If based on more substantial body of data this again might be a useful method in the classification of patients into various disease states.

A copy of the program for the above type of analysis can be obtained from the Department of Epidemiology and Biometrics, University of Toronto. When the number of variables is greater than two, the program can be used to determine the centour for each patient, together with tables for the same purpose.

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SMOKING AND DISEASE

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Historical

It all started in America, and long before the arrival of Columbus — but then the Red Indians smoked a pipe. The European villain of the piece is said to have been Sir Walter Raleigh, though some say that tobacco-smoking was introduced in Europe by Bristol seamen when Sir Walter was still in his boyhood.

However, smoking was not unknown in Europe before the 16th century; Roman remains in Great Britain and Ireland suggest that hemp and aromatic herbs had already been smoked in pipes. During the last War, at least in Malta, the wheel had turned full-circle; because of the shortage of tobacco due to the siege enterprising "addicts" started smoking dried fig, vine and lemon leaves as well. After the second World War, a worldwide rise in the consumption of tobacco occurred, largely due to an increase in smoking by women.

The first inkling that tobacco was definitely harmful to health came from two American retrospective surveys published in 1950 [1, 2, 3, 4], but it was only in 1953 that these reports received widespread publicity in the Press and the general public was at last made aware that there might be a relation between smoking and disease.

The next important step was a large scale prospective study by Hammond and Horn published in the J.A.M.A. of 7th Aug. 1954 [5]. This report showed the effect of cigarette smoking on total death rates, and it included data on the relationship of smoking to ischaemic heart disease and to respiratory conditions other than lung cancer. Subsequent studies showed that these reports had very little effect on the smoking habits of the general population; if there was any reduction of smoking at all, it was largely confined to men with a university education [6, 7].

Many scientific studies on the subject then appeared, but it was not before 1962 (Report of the Royal College of Physicians) and again in 1964 (Report of the Advisory Committee to the Surgeon General) [8, 9] that a definite forward step was taken to give wide publicity on television and radio and in the press, to the harmful effects to health of tobacco smoking and especially of its inhalation.

Most (?) British doctors had stopped smoking for some time [10], but for the first time ever the layman had started to take notice. Figures show that, at least in the U.S.A., the total consumption of cigarettes dropped from 75.2 million packets (of twenty) a day in 1967 to 74.5 million in 1968 ,then to approximately 72.5 million in 1969, despite a population increase of about three million persons per year [11].

However, in 1969 the FAO reviewing the world tobacco economy from 1955 to 1967 reported that "..... the outlook is that tobacco consumption will grow further in developed, developing and centrally planned countries. In the past decade the most remarkable feature of tobacco consumption has been the trend towards cigarettes .The manufacture of cigarettes expanded by one half in developing and centrally planned countries and by 40 per cent in developed countries....." [12]. It appeared that some persons might have stopped smoking, but, if so, those who had not done so must have increased their daily quota of cigarettes.

At its forty-fifth Session held in Geneva in January, 1970, the World Health Organization stated through its Executive Board that "no organization devoted to the promotion of health can be neutral in the matter of cigarette smoking" and "requested the Director-General to report to the Twenty-third World Health Assembly on measures that might be taken to affirm the hazards of smoking". This led to a comprehensive report on "Smoking and Health" [11], written jointly by Drs. C. M. Fletcher ,of London, and D. Horn, of U.S.A., WHO consultants, who reviewed the whole problem suggesting ways and means of "reaching" the public.

In August of this year, at the XI International Congress on Diseases of the Chest, held in Lausanne, Switzerland, no less than two major Symposia occupying two half-days were devoted to smoking problems (office management, biological effects) and to cancer of the lung (epidemiology, case finding, clinical varieties).

Finally, at the Twentieth Session of the WHO Regional Committee for Europe, which was held in Malta during the end of September, 1970, measures for the control of smoking were fully discussed. It was disclosed that the Government of Malta had decided to take statutory and educational measures for the control of smoking.

Hazards of smoking

Comparative mortality. Comparative mortality studies of smokers and non-smokers showed that:

1. Cigarette smokers, taken as a whole, have approximately 30-80% greater mortality than non-smokers [10, 13];
2. The mortality is greater in cigarette smokers who inhale than in those who do not [10, 13];
3. Smokers of pipes and cigars, taken as a whole, have little or no excess
4. Pipe or other smokers *who smoke heavily or inhale* have mortality rates that mortality compared with non-smokers;
are 20-40% greater than those of non-smokers [13, 14];
5. Excess mortality increases with the number of cigarettes consumed *(or more correctly with the amount of tobacco smoke inhaled)* and the length of the smoking history.

Smoking and Disease. It is to be expected that of the excess mortality in smokers 80% would be due to diseases of the respiratory tract, i.e. lung cancer, bronchitis, emphysema. Other conditions in which consumption of tobacco has been proved as a provoking or an etiological agent include ischaemic heart disease and other conditions of the vascular system, peptic ulcer, and cancer of the oral cavity, larynx, oesophagus and bladder. It is also being said that concer of the breast may be more common in wives whose husbands are smokers; this is hard to prove as control trials would create obvious difficulties.

Those who are interested in smoking, financially or otherwise, have brought forward the theory that the urge to smoke and the predisposition to certain diseases are both genetically determined and both combine to produce the diseased state. Proof of this concept is far from convincing.

On the other hand, Fletcher and Horn [11] have stated that smoking has to be accepted as responsible for the increase in incidence or in the severity of a disease if:

a) the incidence of the disease is quantitatively related to the exposure to cigarette smoke;

b) the incidence decreases in those who stop smoking;

c) a mechanism can be postulated by which the disease could be produced or exacerbated by smoking; and

d) the disease can be produced in animals by exposure to cigarette smoke or to its components.

Retrospective and prospective studies from Canada ,the United Kingdom and the U.S.A. [12, 13, 14, 9] as well as from several other countries [9, 15, 16, 17] have shown that the above requisites have been amply fulfilled.

Pulmonary diseases related to smoking

Bronchitis. Some degree of impairment of pulmonary function is invariably present *in all smokers* [9, 18, 19] and 30% of *heavy smokers* (more than 15 cigarettes a day) develop chronic bronchitis [18].

The main abnormalities consist of progressive narrowing of the pulmonary airways and impairment of gas transfer, with consequent hypoxaemia [20] and recurrent bronchial infections. This is due to the many irritants in tobacco smoke causing broncho-constriction and hypertrophy of the mucous glands and paralysing the action of the cilia lining the bronchi; in fact, intensification of cough and sputum shortly after stopping smoking may result from the reactivation of the mucociliary mechanism [21].

When "young" smokers stop smoking early enough, the lung function will usually return to normal, but when bronchitis is advanced and emphysema is established, the lung changes are irreversible.

The above changes have not only been observed postmortem in smokers, but have also been demonstrated in the lungs of rats who are regularly exposed experimentally to inhalation of tobacco smoke [22].

Lung Cancer. Retrospective and prospective surveys have proved convincingly that the effect of tobacco smoking, and this includes cigar and pipe smoking as well, depends only on whether smoke is inhaled or not [23, 24], are definitely related to the risk of developing a certain type of cancer of the lung, with the risk increasing with the amount of tobacco consumed.

Granted that in some types of lung cancer other factors, such as predisposition, air pollution ,industrial hazards as well as geography have to be taken into consideration, one can say that, other than in the case of adeno-carcinoma, lung cancer is self-produced, i.e. by smoking.

Statistics from several countries have shown an increase in the incidence and mortality rates of cancer of the lung during recent decades. In Malta, where very few women smoke, and most men do and where industrialization is still in its infancy the number of men reported as having cancer of the lung in 1969 was more than double that of 1952 (when all forms of cancre became notifiable by legislation), i.e. 1952, 23 new cases; 1969, 56 new cases but during the same period there has not been any change in incidence in the case of women, i.e. 1952, 6; 1969, 4. Again, in 1969 the mortality from cancer of the lung was the highest of all deaths due to cancer — 75 (66 men and 9 women) out of 368 cancer deaths. This, coupled with the fact that cancer of the lung has increased in frequency in both sexes in countries where women smoke [13], may be taken as further evidence of the relation between smoking and lung cancer.

Postmortem studies have shown that the bronchi of cigarette smokers show extensive metaplastic changes which could be precancerous[9]. These metaplastic cells are particularly extensive when lung cancer is present, while they tend to degenerate in ex-smokers, which might indicate regression of pre-cancerous changes [11].

Experimental evidence is not lacking. That cancer of the skin can be readily induced in animals by the local application of condensates from tobacco smoke (cigarette, cigar, pipe) has been known for some time. Quite recently, squamous cell carci-

noma of the lung has been induced in dogs by making them smoke through a tracheostomy tube [11].

As yet not all the substances that are of prime importance in the production of cancer have been identified; nevertheless, it is well known that benzo-pyrene is a cancer "initiator" and that it occurs in the highest concentration in tobacco smoke.

The effect of cigarette smoking on *pulmonary tuberculosis* is not clear. It is a fact that in spite of widespread increase of smoking in highly developed countries the incidence and mortality from pulmonary tuberculosis have been rapidly declining.

On the other hand, cigarette, pipe and cigar smokers hav a four-fold higher risk of dying from cancer of the *mouth, larynx, and oesophagus* than non-smokers [19].

Other diseases related to smoking

The evidence that smoking is a contributory cause to *diseases of the arteries* is not so strong as in the case of pulmonary diseases. Nicotine is the provoking agent and absorption takes place through all the mucous membranes and inhalation is not necessary for the production of adverse effects on the circulatory system.

It is doubtful whether smoking can cause *peptic ulcer*, but it certainly causes pain in ulcer patients and delays healing of the ulcer.

The relation between cancer of the *bladder* and smoking has been proved. Recently, independent studies have shown that smoking during *pregnancy* is detrimental to the foetus: newborn babies weigh less and the risk of abortion, stillbirth and peri-natal mortality is increased two-fold [25].

Actions and reactions

What has been done in the face of all the evidence?

The tobacco manufacturers are doing their level best to advertise and to promote their wares by coupling cigarette smoking with all that is healthful and desirable in life, i.e. outdoor life, all kind of sports, the female form, etc. To the critics they reply that their aim is not to seduce non-smokers but to try to induce smokers to change over to the particular brand advertised.

Most countries have already abandoned their neutrality and have risen to the responsibilities by banning the advertising of cigarettes on television and radio in various ways:

a) *Complete ban:* Czechoslovakia, Italy, Switzerland, France, United Kingdom, U.S.A. (as from 2nd January, 1971), Denmark, Norway, Sweden, Australia and Canada (Canadian Broadcasting Corporation Network, several independent stations).

b) *Partial ban:* Canada, Federal Republic of Germany, Finland (complete ban by the end of 1970).

c) *Phased elimination*: Ireland (complete ban by March, 1972), Argentina (also in cinemas) for a one year period.

In Malta, on the 23rd of October, 1970, in the House of Representatives, Dr. A. Cachia Zammit, Minister for Health, moved the first reading of a Bill to control the advertising of tobacco; the Bill was given a second reading on the 27th of the same month.

Meanwhile, the confirmed smoker, and therefore the one most at risk, is puffing away to his heart's content..... or discontent.

Preventive measures

Fletcher and Horn [11] rightly state that to reduce the death and disability that result from smoking, a programme should aim at *three main objectives:*

1. to discourage young people from starting to smoke;
2. to reduce the number of people now smoking;
3. to encourage the development of less hazardous cigarettes and methods of smoking and at the same time to persuade smokers to turn to them.

Of the several possible ways leading to the first objective, it is felt that the most effective would be:

a) to educate the young by all the

means and media available, especially by television and the cinema, about the dangers of smoking;

b) to discourage smoking in the presence of non-smokers;

c) to abolish *all* kinds of tobacco advertising.

Admittedly, objective number two is the hardest to achieve. It is said that tobacco smoking is an addiction, but "addiction refers to alteration in the body's biochemistry resulting from exposure to a drug. There is little evidence that basic alterations of this nature play any significant role in cigarette smoking" (21).

Smoking is certainly a "bad" habit, and as with all such habits difficult but not impossible to break. In this respect half-hearted measures are worse than useless, and, besides adopting measures already mentioned, more drastic steps should be taken to "help" the confirmed smoker to overcome his habit. Smoking should not be allowed in public places and should be absolutely forbidden in Government Departments. Private enterprise should be persuaded to follow this lead. Smoking has not been permitted at the Chest Clinic at St. Luke's for some years now, and Chest and Heart posters on the dangers of smoking are on view at the entrance to the Clinic.

Several attempts have been made to make smoking less hazardous to health. Tobacco monopolies in Canada, Sweden, U.S.A., Austria and Japan have lowered the amount of tar and nicotine content in tobacco. Others have claimed that special filters appear to give protection against particulate matter in smoke, but there may be other harmful chemicals in tobacco smoke which are unaffected by filters (21). Discarding the last third of the cigarette, where a high concentration of tar and nicotine accumulates, helps to reduce the amount of harmful substances inhaled. Some have advocated a substitute for tobacco, while in a recent letter to the "British Medical Journal" it was suggested that smoking of nicotine alone should help to replace the cigarette (26).

But the only certain protection is not to smoke at all; after all "If the Almighty had meant you to smoke, he would have put a chimney in your head."

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BOOK REVIEW

Malta Case Study — A Preliminary Study of the Nutritional Status of the Maltese Islands. F. F. Fenech, A. Grech, A. P. Jaccarini, L. Vassallo and P. Vassallo Agius, 21st October, 1970. Cyclostyle. pp. 43, Royal University of Malta.

The *Malta Study* represents part of the contribution of Maltese participants in the First Commonwealth Conference on Development and Human Ecology held at the Royal University of Malta, Msida, between the 18th and 24th October 1970. It is a detailed survey of the nutritional state of the children and adults of our Islands. Owing to the insufficiency of human biological data of Maltese society, the authors had to rely, in the main, on indirect methods of assessing the nutritional conditions of the community, such as the infant mortality rate and the morbidity and deaths due to respiratory and gastro-intestinal infections. The authors have reached the happy conclusion that Maltese children do not suffer from undernutrition nor die from intercurrent diseases associated with it and that in this sector Malta takes its place among the better developed countries.

The problem posed by adults is that of excessive alimentation. A pilot study of one hundred randomly sampled Maltese households bears out the fact that obesity, with its aggravating role in the incidence of cardiovascular diseases, "is a serious national problem" calling for a course of preventive action at community level aiming, principally, at educating the young on the dangers of overfeeding.

The *Malta Study* is an excellent piece of field work in the health sector of Maltese social life. Apart from its intrinsic value it affords clear proof that team work among members of the Maltese medical profession is not only feasible but is the most fruitful way of investigating health problems on a national scale. It is, furthermore, an outstanding example of how the different outlooks of medical men working in separate fields can be harmoniously merged and integrated giving a holistic approach towards the study of man in his internal and external environment.

We look forward eagerly to seeing the publication of the results of the full survey of one thousand four hundred households which the authors propose to carry out.

PAUL CASSAR.

PUBLICATIONS LIST ...

The following are recent publications by graduates of our medical school:

CAUCHI, M. N. (with CLEGG, J. B. and WEATHERALL D. J.) 1969. Haemoglobin F (MALTA): A new foetal haemoglobin variant with a high incidence in Maltese infants. Nature. *223*, 311.

CAUCHI, M. N. 1969. Thalassaemia, Glucose-6-Phosphate Dehydrogenase Deficiency and abnormal haemoglobins in the Maltese population. Med. J. Aust., *2*, 1315.

CAUCHI, M. N. 1970. The incidence of Glucose–6–Phosphate–Dehydrogenase deficiency and Thalassaemia in Malta. Brit. J. Haemat., *18*, 101.

CAUCHI, M. N. (with DAWSON, K. B. and FIELD, E. O.) 1970. Relationship of Graft versus Host Disease and Oncogenesis, in "Proc. IV Quadriennial Int. Conference on Cancer-Immunity and Oncogenesis".

CAUCHI, M. N. 1970. Immunological Studies on Tumours arising from a graft versus host reaction. Aust. Soc. Exp. Path., Annual Meeting, 1970.

GRECH, P. (with BEVIS, D. C. A.) 1969. Foetal myelography — an unusual complication in intrauterine transfusion. Br. J. Radiol., *42*, 389.

GRECH, P. (with CROALL, J.) 1970. Radiological maturity of the small-for-dates foetus. J. Obstes. Gynaec. Brit. Commwlth., *77*, 802.

GRECH, P. (With CROALL, J.) 1970. Hyperflexion of the small-for-dates foetus. *Ibid.*, *77*, 808.

VASSALLO, L. 1970. Murine typhus in the Maltese Islands. Ann. trop. Med. Parasit., *64*, 153.

VASSALLO-AGIUS, P. (With RUSHWORTH, A. and COONNOLLY, N.) 1970. Case Report: Anomalous origin of left coronary artery associated with an aorto-pulmonary septal defect. Brit. Heart J., *32*, 708.

MEDICAL NEWS

The shattering news of Professor Alfred John Craig's tragic death has by now reached almost everyone in his very wide circle of friends. Apparently taken ill while driving in Valley Road, Msida, soon after leaving St. Luke's, he crashed into a wall and was killed almost instantly. Certainly none of us will forget the morning he was brought into "casualty", beyond reach of such help as he had so often lavished on others. At the church service next morning the fairly large hospital chapel was literally crammed by persons in every walk of life, from H.E. the Governor-General downwards. It was remarkable that every person present looked upon John Craig as a personal friend and, among the crowd, endless stories were told of his kindness and of the solicitude with which he looked after his patients such as, to quote but one, of an occasion when he visited a child six times in a day to be able finally to decide that his patient did not have appendicitis.

At the funeral we saw such a gathering as we had never seen before, including a vast number of non-medical people. In one way or another every person there owed him a deep debt of gratitude. Mr. Michael Spiteri published some very touching lines in a poem entitled simply "Craig" in "Il-Hajja" for the 9th October. He wrote:

"U reġa' radd lura l-għarusa lir-raġel,
u reġġa' 'l missier f'dirgħajn martu u wliedu;
eluf reġġa 'lura minn xifer il-mewt."

The profession has also suffered bereavement through the death of Dr. John Cesareo, of Floriana, an extremely well-liked practitioner who had throughout his life special interest in maternity work, and of Dr. Irene Condachi. Dr. Condachi retired some years ago from her place as a School Medical Officer. She was something of a pioneer, having been one of the first ladies to practise medicine in Malta. She had qualified in Naples in 1926 .The sudden death of Professor Harry Micallef, who occupied the chair of Biology, deeply grieved all his friends in medical and university circles.

We congratulate Dr. Paul Cassar, a frequent and valued contributor to the Gazette, for being the first person to be elected an Honorary Fellow of the Royal University of Malta; Dr. Anthony Jaccarini on his election to the Fellowship of the Royal Institute of Chemistry; Dr. F. F. Fenech and Dr. Luis Vassallo on their election to the Fellowship of the College of Physicians of Edinburgh; Dr. Pio Mangion, now Medical Registrar at lovely St. Peter's Hospital, Chertsey, Surrey, on getting his M.R.C.P. (U.K.); Dr. Albert Schembri-Wismayer on getting the Diploma in Medical Radiology (Diagnostic); Dr. Norman Griscti-Soler on being awarded the Ph.D. His main work has been on diabetes, carried out in Birmingham, whilst on a Commonwealth scholarship.

The Malta Branch of the B.M.A. is, as usual, very active. On the 29th July Dr. A .H. W. Babington of the artificial limb centre at St. Mary's Hospital, Portsmouth, and formerly of Roehampton, lectured on "Rehabilitation of Lower Limb Amputees" and showed a film on the subject. The Branch, profiting by Professor Marjan Weiss's presence in Malta in connection with the meeting of the W.H.O. regional committee for Europe, invited him to lecture on "Physiological Amputation" which he did on the 30th September. He also showed a film on "Rehabilitation of the paralysed Child". Professor Weiss, who is Polish, is the Chairman of the Institute of Reconstructive and Rehabilitation Surgery at the Warsaw School of Medicine and adviser on Rehabilitation to W.H.O. Both Dr. Babington and Professor Weiss's films were oustandingly interesting. Professor Weiss's method relies on the quick fitting of the prosthesis soon after operation. This has many advantages including, said Professor Weiss in answer to a question, the avoidance of the development of phantom pains.

The St. Luke's Day lecture was given by Dr. Paul Xuereb LL.D., librarian to the University, dramatic critic and himself no mean actor. It dealt with "The Doctor and the Stage". Since it was erudite and full of uncomplimentary references (by the playwrights quoted, not by the lecturer)

to the profession, it was greatly enjoyed. The delivery of the lecture was preceded by a brief commemoration of Professor Craig by the Chairman.

The B.M.A. Medical Essay Prize was awarded this year to Dr. Paul Cassar for his long paper on "Medicine in Malta 1800-1810". One has got so used to the excellence of Dr. Cassar's work that one tends to take the huge amount of work and research which it involves for granted, but it is there all the same.

The W.H.O. Regional Committee for Europe met for its twentieth session in Malta, from the 22nd to the 26th September. There was a 7-man Malta Delegation and papers were also read by Maltese physicians. The business meetings were held at the Malta College of Arts, Science and Technology. A good entertainment programme was also laid on and everything went along very successfully. In a fit of nationalistic zeal, however, the delegates had a programme of all-Maltese music inflicted on them at the Manoel. To convince our guests that music can be made in Malta is all very well but to show them we are fully civilised we should also give evidence that we can play and can appreciate the classics. The University gave an honorary LL.D. to Dr. Marcolino Gomes Candau, the Director General of the W.H.O.

Under the auspices of "The Association of Physicians and Surgeons of Malta" and the sponsorship of the firm Boehringer Ingelheim, Professor J. B. L. Howell showed a film and lectured on "Breathlessness" on the 30th October. Both were of an extremely high standard and held the audience's attention.

With the death of Professor Egidio Lapira on the 7th December, the dental profession in Malta lost its doyen and its founding father. Professor Lapira was a man completely dedicated to his work and he strove at every time to advance the Dental Surgeon's status in Malta. The first occupant of the Chair of Dental Surgery in our university, he was the recipient of many honours, including a D.Sc. *(hon. causa)* bestowed on him at his retirement. He was the life president of the Malta Dental Association, which he had founded as long ago as 1926 and was an honorary vice-president of the International Dental Federation.

We congratulate the following, on graduating in Dental Surgery: Mr. Michael Abbott of Brisbane, Australia; Mr. Alfred Magri Demajo, of Hamrun (who was also awarded the Amalgamated Dental Prize); Mr. Alfred Pace Balzan of Sliema; Mr. Klaus Vella Bardon of Birkirkara; Mr. Paul Vella of Pawla; and Mr. Cheng Choy Soon, of Malaya.

Mr. John Portelli has been awarded the M.D.S. in Dental Prosthetics in 1970 by the University of Manchester. Mr. Klaus Vella Bardon has been awarded a W.H.O. scholarship to attend the Course in Dental Public Health at the Dental School of the University of Dundee.

Dr. Charles Olivieri Munroe is now taking up the post of Associate Professor in Oral Medicine at the Dental School of the University of Toronto.

Dr. Alfred Grech, of the Health Department, is one of the writers of a long and comprehensive report, published by the European Public Health Committee of the Council of Europe, issued at Strasbourg this year, on "Structure and Organisation of Road Accident Prevention, with reference to the Medical Aspects of the Problem". Dr. Grech was a member of a 5-man team who carried out a study dealing with health education and research, visiting Austria and Britain in connection with this.

Mr. Charles Boffa has published his most ambitious work so far "The Second Great Siege. Malta 1940-1943" (Printed at the St. Joseph Home, Hamrun). It is a very good record of the most glorious part of our history which, for many reasons, should never be forgotten. Mr. Boffa deserves our gratitude for putting so much on record.

Professor Jack Adams-Ray, professor of Surgery at the Karolinska Institute and head of the department of Surgery at the Karolinska Hospital in Stockholm, in Malta on holiday, broke into his period of relaxation to give three excellent lectures, one on "Treatment of Burns" on the 23rd

November, one on the 27th on "Cathecolamines in Surgery" as the concluding talk in the 1st Annual meeting of "the Association of Physicians and Surgeons", and the third on "Sunlight and Cathecolamine production (with effect on Psoriasis)", on the 30th under B.M.A. auspices. Professor Adams-Ray is Swedish with a Scottish ancestry, which probably explains his engaging dourness, lit by flashes of humour. He told the story of how he successfully patched up a soprano in time for her to go on stage and thus save a performance of "Tannhauser", asking (jokingly, of course) for 10% of the proceeds of the performance for his services. Many members of the profession had an opportunity of meeting him soon after he arrived, at a wonderful party at Dr. and Mrs. Raphael Attard's lovely new home at Tal-Virtù.

At the first Annual meeting of "The Association of Physicians and Surgeons of Malta", held at the Medical School on the 27th November, under the chairmanship of Professor J. V. Zammit Maempel, the following papers were read: "Poisoning in Children in Malta" by P. Vassallo-Agius and H. M. Lenicker; "Aspects of Typhoid fever in Malta" by L. Vassallo; "Familial bleeding disorders in Malta" by J. Rizzo-Naudi; "Hospital Mortality in Acute Myocardial Infarction" by F. Fenech; "Holt-Oram syndrome in a Maltese Fomily" by C. Jaccarini, F. Fenech and P. Vassallo-Agius; "The Oral cavity. Its rôle in cardiac disease" by G. Camilleri; "Analysis of 36 cases of Cancer of the rectum" by R. Attard and J. B. Pace; "Retroperitoneal tumours" by J. Muscat and Marie Therese Podestà; "The problematic pill" by M. Elder; and "Newer methods of safeguarding the foetus in the later stages of pregnancy" by L. German.

The first Commonwealth Conference on Development and Human Ecology was held here between the 21st and the 24th October. Amongst the participants was Lord Douglas, a former governor of Malta. A group of doctors presented a report on local nutrition problems, which is reviewed elsewhere in this issue.

Professor Arthur P. Camilleri gave the address at the Opening Day ceremony of the University, speaking on "The University and Forces of Change". We don't think he made the best use of his opportunity to trounce educational faddists, but all in all it was a stimulating oration.

Prof. P. Mascherpa of Pavia lectured on "Physiological Anti-infectious Substances" on the 29th October, under the aegis of the "Medical Association of Malta".

All things considered we can't think anybody could consider life in Malta to be stagnant nor could its worst enemy accuse the local medical profession of lethargy.

Summer visitors to the old country included Dr. Paul Bonnici from Santa Monica, California and Dr. F. Demanuele from Toronto. Dr. Demanuele lives in Spadina Road: mysteriously everything seems to happen in Spadina Rd. in Toronto. Its names fascinates and mystifies us.

A small group of Italian doctors met at the Hilton Hotel on the 17th October for a "round table" at which the Medico-Social Aspects of Obesity" were discussed. There was Professor Gino Bergami from Naples University, Professor Carlo Bianchi of Parma, Professor Ermanno Lanzola of the Institute of Hygiene of Pavia and professor Marcello Proja of the Italian Ministry of Health. Local doctors were also invited. The meeting started at about 10 p.m. and went on to about one o'clock in the morning, which was something of an endurance test which many did not even attempt to pass. This gathering was sponsored by "Minerva Medica", itself a sponsored periodical.

We have been informed that the Italian Society of Pathology has invited the European Society of Pathology to hold its 3rd Congress in Italy on September 14-16, on the occasion of the second centenary of the death of Giovan Battista Morgagni.

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