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13th Alexander Brown Memorial Lecture given on 22 February 1985 by G. Onuaguluchi

Introduction by Professor A. O. K. JOHNSON, *Provost*
College of Medicine, University of Ibadan, Nigeria

Introduction

When this Medical School started in 1948 as one of the foundation faculties of the new University College, Ibadan, a young, dynamic and very energetic Scot was appointed from Edinburgh to be the foundation Professor of Medicine. Dr Alexander Brown arrived here not knowing exactly what to expect. However, he launched himself into his new job with great zeal and enthusiasm. The foundation of our present Department of Medicine was laid by him at Adeoyo hospital, and the eminence that the Department rapidly achieved in terms of men and material that emanated from there, is a testimony to his total commitment. For 21 years, Professor Brown contributed in great measure to building a Medical School, and indeed a University we all are very proud of today. He realized the need for the expertise and high-level manpower available in a place like this to be used in the community for the community, and he appreciated very early the need for primary health to be a major orientation in our curriculum, and our health planning, and he is generally regarded as the founding father of the Ibarapa Community Heath Project. He was an outstanding teacher, an astute clinician and a proven administrator. Apart from being the Head of the Department of Medicine for several years, he was Dean of the Faculty of Medicine in 1949–50, and again in 1952–56. He served as a member of the old Provisional Council and later of the formally constituted Board of Management of the University College Hospital. He also acted as Vice-Chancellor several times and was a member of the University Governing Council.

When Professor Brown died quietly in his sleep in 1969, the then Vice-Chancellor set up a Committee to recommend ways of immortalizing the late Professor. The recommendations included the endowment of this Memorial Lecture. A prize was also founded to be awarded for the best essay from any medical school in Africa. The Clinical Students' Hall has also been renamed the Alexander Brown Hall.

The first Alexander Brown Memorial Lecture was given in March 1972 by the late Dr A. A. Quenum, then Regional Director of the World Health Organization and his topic was 'Medical Education in Developing Countries'. The lecture has been given every year since then by very eminent scholars in medicine, all of whom were either late Professor Brown's schoolmates or colleagues at work, and included such very eminent scholars as Sir Melville Arnot of the University of Birmingham, Professor H. C. Kodilinye, then Vice-Chancellor of the University of Nigeria, Nsukka; Professor Scarborough, then Dean, Faculty of Medicine, Ahmadu Bello University, Zaria; Dr Trevor Kinnear, former Professor of Medicine, University of Ibadan and now Consultant Physician in Hull, U.K.; Professor J. C. Edozien, Professor and Chairman of the Department of Nutrition, School of Public Health, University of North Carolina, U.S.A. and a former Dean of Ibadan Medical School; and Professor T. O. Ogunlesi, Professor of Medicine in the University of Ibadan and first Director of the Ibarapa Programme. Others included Professor F. Dudley Hart, a classmate of Professor Alexander Brown in the University of Edinburgh in the early 1930s; Professor C. Nwokolo, Professor of Medicine at the University of Nigeria Teaching Hospital, Enugu and Professor Brown's first House Physician in Nigeria; Professor A. O. Lucas, former Head of our Department of Preventive and Social Medicine and now Director of the Tropical Disease Research Programme of the World Health Organization in Geneva; Professor

O. O. Akinkugbe, former Head of our Department of Medicine, Dean of our then Faculty of Medicine and thereafter Vice-Chancellor of the Universities of Ilorin and Ahmadu Bello, Zaria. Professor T. I. Francis of our Department of Medicine who is currently the Vice-Chancellor of the Federal University of Technology, Akure gave the 12th lecture in 1984.

Today we have no less a distinguished academic scholar to deliver the 13th Alexander Brown lecture. Professor Onuaguluchi is the doyen of Clinical Pharmacologists in Africa. He was Professor Brown's House Officer and later his Consultant colleague here at UCH. Professor Onuaguluchi rose to become the first Professor of Clinical Pharmacology in this University, a post he held from 1965 to 1966. He has also been Dean of the Faculty of Medicine, University of Nigeria and Vice-Chancellor of the University of Jos. He is presently Professor and Head of the Pharmacology and Therapeutics Department, University of Nigeria, Enugu Campus.

It is my honour and privilege to call on Professor G. Onuaguluchi to give the 13th Alexander Brown Memorial Lecture: 'Cardiotonic Drugs in the Management of Chronic Congestive Heart Failure: Digitalis Revisited'.

The lecture

The Vice-Chancellor, The Provost of the College of Medicine, Deans of Faculties, Heads of Department, Professors, respected academicians, ladies and gentlemen. I feel most highly honoured to be asked to deliver this year's Alexander Brown Memorial Lecture. I must thank the Head of the Department of Medicine and his colleagues for nominating me, and the Provost for approving the nomination.

I must confess that when I saw the list of the eminent persons who had given the previous lectures, I felt somewhat unequal to the task. I should really at this juncture apologize for my inadequacies but I hope that you will bear with me throughout the period of this lecture.

I am extremely privileged to be delivering this lecture in memory of Late Professor Alex Brown — a great physician, a most distinguished and dedicated medical educator and administrator. Alex Brown was one of the first four professors appointed by London University for the Faculty of Medicine of the University College, Ibadan, which was in special relation with London University.

Prof. Brown arrived in Lagos in late 1948 and I had the privilege of being in the first class of students to whom he gave his first lecture in Medicine as the first Professor of Medicine in this University. I was then a First Year Clinical Student at the School of Medicine, Yaba. By that time, it had been decided that the Faculty of Medicine of the University College, Ibadan, should take over the medical students of the School of Medicine, Yaba. Brown did not stay long in Lagos: he soon left for Ibadan and the class was happy to meet him there in January 1949 when the clinical section of the Yaba School of Medicine was transferred to Ibadan. Figure 1 is a photograph taken at the end of the 1948/49 academic year and shows all the clinical students (three classes) of the School of Medicine, Yaba, who transferred to the University College at Ibadan, and some of their teachers including Prof. Brown.

Prof. Brown was a born teacher. He believed that the clinician must have a solid knowledge of physiology and pathology, and I remember his presence with us at post-mortem examinations whenever a patient of his with interesting but baffling clinical features died. Prof. Brown was lucky to have as Professor of Pathology, Professor Silvera who also came from Edinburgh. Alex Brown did not believe in giving very many lectures: he taught at the bedside, and the interesting stories he told during his long ward rounds about previous clinical experiences helped us to understand medicine and more importantly to perform creditably at the professional examination in medicine.

The class was also most impressed with the fact that Alex Brown, who was a well known teacher at the School of Medicine, Edinburgh University, did not consider us inferior students to the ones he had taught at the Royal Infirmary, Edinburgh. The class had had some bitter and most humiliating experiences from some young pathologists who had started teaching pathology at Yaba. I can clearly recollect one of them, who had only the MB and BS degrees and, I believe, had not quite completed his training in pathology, telling us in a most arrogant manner that we should consider ourselves very lucky to be taught by him because, on qualification, we were to receive only the

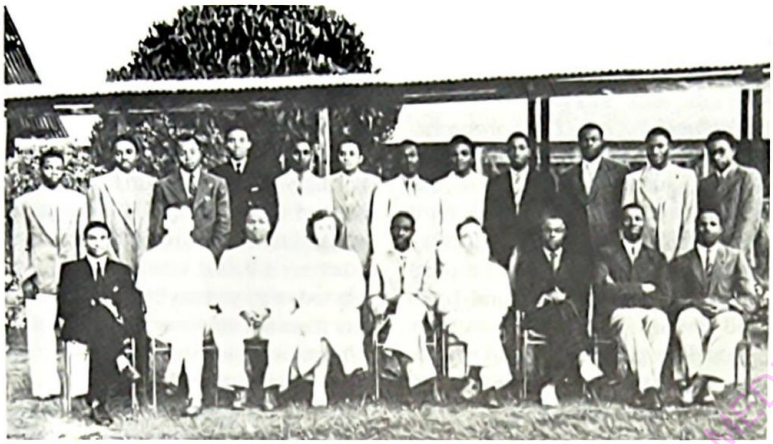

Fig. 1. Photograph of clinical students from The School of Medicine, Yaba, and some of their university teachers at the end of the 1948/49 academic year. Sitting left to right: S. L. Adesuyi, Dr H. Walker; A. A. Azie; Prof. Beatrice Jolly; V. G. Ene; Prof. Alex Brown; J. O. J. Okezie; Prof. O. Ajose; A. Okuboyejo. Standing left to right: M. O. E. Thompson; M. U. Ozo; A. C. Anazonwu; M. S. G. Douglas; F. A. Olapade; E. B. Ekong, K. Diete-Spiff; G. Onuaguluchi; F. S. Obioha; J. Nwokolo, P. Ofili; L. C. D. Beregha.

local Yaba Diploma which had no value internationally, and even locally it only entitled one to an Assistant Medical Officer appointment in the first instance. I must personally, on behalf of the class, publicly express our profound gratitude to this great teacher for making us feel that we were as good as his students in Edinburgh and also for his superb instruction and personal interest in us when we studied under him as undergraduates.

Prof. Brown really built this internationally renowned medical school, now part of the College of Medicine of the University of Ibadan. He was Dean of the Medical School on a number of occasions and often acted as Vice-Chancellor. He was heavily involved in the planning of the University College Hospital (UCH), Ibadan — a very well designed teaching hospital complex. I remember how happy he was, as indeed were all of us who were present in 1954, at the Foundation Stone Laying Ceremony at the permanent site of the UCH. I was then a resident at the UCH based at Adeoyo Hospital, Ibadan. It is therefore most fitting that the Hall of Residence for medical students at the UCH is named after this great pioneer medical teacher at this University.

Although Prof. Brown was originally a Senior Lecturer in therapeutics at Edinburgh and finally Professor of Medicine at Ibadan, he was most interested in community medicine and it is on record that he was largely instrumental along with late Prof. K. Dike — the then Vice-Chancellor of the University of Ibadan — in securing outside grants for the Igboora Project (the pride of this College of Medicine) for the study of diseases in the rural population.

Prof. Brown did not personally conduct much sophisticated research but he certainly inspired those who came to work under him. Prof. Adetokunbo Lucas, now of the WHO, spoke in the 10th Professor Alexander Brown Memorial Lecture of how he went into public health and community medicine as a result of the inspiration and encouragement he received from Prof. Brown. I was his House Officer in 1954 and by that time he had become very interested and was most involved with the treatment of pulmonary tuberculosis which was then a very major killer disease. He had perfected the technique of artificial pneumothorax and pneumoperitoneum, and with Dr Laukner, who was then a Lecturer in Medicine, we ran a very busy TB clinic with refill sessions for these patients. I became so interested in this work that I decided to train in chest diseases and, when I had the opportunity, I studied chest

diseases at the famous Institute of Chest Diseases, London University and Brompton Hospital, London. I later obtained the MRCP Edinburgh with respiratory diseases as my special subject.

Prof. Brown was also a personal friend. Those of you who were on the staff of this medical school between 1962 and 1966 must remember with some nostalgia Prof. Brown's most convivial house parties. I was a frequent guest at these parties and my wife and I still remember and cherish the happy times we spent with him and his guests. It should now be easy for you to understand why I should feel most elated to be asked to give this lecture in honour of my late teacher, friend and later colleague.

Now to the topic of my lecture. It was not easy to select the topic. On looking at the titles of previous lectures, it would seem that most of them dealt with aspects of medical education in Nigeria and the role of the Ibadan Medical School in the development of undergraduate and postgraduate medical education in Nigeria. However, although I have had some experience in medical school administration: I was an Associate Dean at this medical school; as Dean of Medicine in collaboration with many dedicated colleagues, founded the Enugu Medical School soon after the Nigerian civil war; and as Vice-Chancellor of the University of Jos, was much involved with Prof. Alfred Ikeme (another former Ibadan medical teacher) in founding the Jos Medical School, I was convinced, for reasons which will soon become clear, that I should not speak on medical education despite Prof. Brown's pre-eminent role in the development of the Ibadan Medical School.

Prof. Brown was a physician who, before coming to Ibadan, taught therapeutics at Edinburgh. I am also a physician teaching pharmacology and therapeutics and I felt therefore that one should speak on some aspects of drug therapy of a major disease state.

Apart from pulmonary tuberculosis, another disease which I believe took up Prof. Brown's time was chronic congestive heart failure. Indeed the Ibadan Medical School has been in the forefront in the study of cardiovascular diseases in Nigeria and we have such names as Abrahams — a major pioneer, Ikeme, Adi, Parry, Akinkugbe, Antia, Brockington, Carlisle, Salako, Cole and one of my most brilliant former students — Prof. A. Falase. Prof. Brown was the prime mover; he spared no efforts in seeking and obtaining the services of the right kind of staff and generally encouraged and inspired them.

The year 1985 also marks the 200th anniversary of the introduction of digitalis leaf in the management of cardiac failure. I was therefore convinced that it would not be out of place if I shared with you my thoughts and the results of my research on some aspects of drug therapy of chronic congestive heart failure with digitalis and other cardiotonic drugs.

This lecture will deal with some aspects of the biophysical changes (mainly changes in cardiac mechanics and electrical activity) induced by cardiotonic drugs used in the management of chronic congestive heart failure. I will endeavour to show how consideration of the biophysical and haemodynamic changes induced by these cardiotonic drugs created doubts about the appropriateness of the use of cardiotonic drugs in increasing cardiac output in chronic congestive heart failure.

As some of you know, my book published by Butterworths of London in 1964 was on Parkinson's disease, and during my stay at Ibadan I showed some interest in the pharmacology of remedies used in traditional medicine, but these remedies were not for the treatment of cardiovascular diseases. However, during my 1 year sojourn in the U.S.A. as a Visiting Professor of Pharmacology at the University of Oregon, Health Sciences Centre, I became associated with Dr Ralph Tanz who had done considerable work in cardiovascular pharmacology, and on his kind invitation, I used the facilities in his laboratory.

As you are all aware, in 1785, Withering introduced, as a remedy for dropsy, digitalis leaf which was one of the components of a medicinal preparation used by a Shropshire woman for the treatment of dropsy. It is therefore most surprising that by 1979 no other cardiotonic drug had been found useful in the treatment of chronic congestive heart failure. A number of substances had, however, been studied for their possible use as cardiotonic drugs in the treatment of congestive heart failure. They include dopamine, dobutamine, steroids, glucagon, ionophores, anthropleurin A, etc., but none of them was found useful in

the management of chronic congestive heart failure.

Although digitals has been unrivalled for nearly 200 years as a cardiotonic agent in the treatment of chronic congestive heart failure, it is very prone to inducing dangerous cardiotoxic effects including ventricular tachycardia and severe heart block. The serum therapeutic levels for digoxin and digitoxin are 1–2 ng/ml and 20–30 ng/ml, respectively, and yet the toxic serum levels are ≥3 ng/ml and ≥45 ng/ml for digoxin and digitoxin, respectively. Indeed, it is estimated that at least 60% of the toxic dose is required to produce a therapeutic effect [1]. The therapeutic index is thus very low and the safety margin is often less than 2.

It was therefore necessary to continue the search for much safer yet effective cardiotonic agents that might provide alternatives for the treatment of chronic congestive heart failure. You can therefore imagine the intense expectations which were aroused in 1978 following reports [2–5] that amrinone, a bipyridine derivative (Fig. 2) had positive inotropic action *in vitro* and *in vivo* in experimental animals and that it produced salutary haemodynamic effects without inducing changes in heart rate or ECG in patients with chronic congestive heart failure who were not improving on digitalis and diuretic therapy. The electrophysiological patterns in isolated Purkinje fibres or papillary muscles of the cat were found to be unaffected by amrinone. Moreover, the drug was found to be effective following oral administration although it can also be administered intravenously. The interest in amrinone was intense in the U.S.A. and some had begun calling amrinone a wonder drug, more so because its mode of action could not be elucidated.

I was therefore most delighted to study the pharmacological properties of amrinone. At the time I started this work in 1979 only three scientific papers on this drug had been published but the mode of the inotropic action was not elucidated. At this juncture I acknowledge the technical assistance of Mr John A. LaRue and Miss Virginia Sharp. I also gratefully acknowledge Dr A. Alousi of Sterling Winthrop Research Institute, Renselaer, New York, who provided the samples of amrinone.

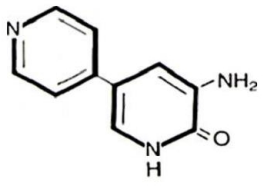

Fig. 2. Chemical structure of amrinone.

The first aspect of this work looked at the effects of amrinone on rabbit papillary muscle and guinea-pig Langendorff heart preparations. The results of this study have been published [6,7].

The study showed that amrinone (50–1000 μg/ml) produced a dose-dependent inotropic action on the rabbit papillary muscle. Amrinone also abolished the hypodynamic state following prolonged stimulation, the contractile force remained significantly elevated over drug-free controls throughout the ensuing 4 h exposure. Figure 3 shows the typical effect of amrinone (1 mg/ml) on the hypodynamic state which follows 4 h continuous stimulation of the rabbit papillary muscle. This is similar to the results obtained by Gold in 1946 who studied the effect of strophanthin on the isolated cat papillary muscle. However, dysrhythmic phenomena occasionally appeared in our preparation when the concentration of amrinone in the bathing fluid was 1 mg/ml. The dysrhythmia were bigeminal, and showed automaticity and an elevated threshold to electrical stimulation. Bigeminy was, however, abolished by raising the stimulating voltage or by increasing the external K^+ concentration in the bathing fluid.

In the isolated Langendorff heart preparation, amrinone (50 μg/ml) induced statistically significant increases in cardiac work (17.2%), coronary flow (49%) and myocardial oxygen

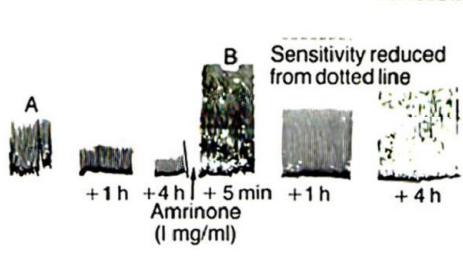

Fig. 3. Rabbit papillary muscle preparation: effect of amrinone (1 mg/ml) on the hypodynamic state induced by continuous electrical stimulation.

consumption, MVO_2 (30%), after 15 min of exposure to the drug. Experiments in which amrinone was allowed to act for 60 min, after which the heart was perfused with drug-free perfusate, showed that the effects of amrinone, unlike those of digitalis glycosides, were easily reversed. Figure 4 shows the results in one such experiment.

Because of the dysrhythmic phenomena which amrinone induced in the isolated rabbit papillary muscle preparation, and the fact that in fully digitalized human volunteers, De Guzman *et al.* [4] found that amrinone (2 mg/kg), while augmenting cardiac performance, decreased the duration of electromechanical systole, it was thought necessary to ascertain whether amrinone would produce ECG changes in the isolated spontaneously beating guinea-pig Langendorff heart preparation, and whether there would be a correlation between the type of ECG changes and the concentrations of amrinone in the perfusate. Consequently three concentrations were studied, namely 50 µg/ml (which earlier was found to produce between 20 and 30% increase in contractile force), 250 µg/ml and 1000 µg/ml, in an attempt to determine the safety margin of amrinone [8].

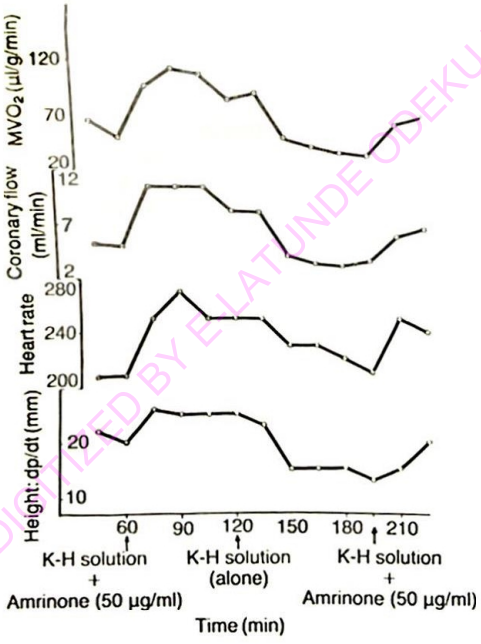

Fig. 4. Guinea-pig Langendorff heart preperation: time course of effects of adding amrinone (50 µg/ml) on MVO_2, coronary flow, heart rate and dp/dt, and the effect of washing off the drug.

Details of ECG changes produced by amrinone were evaluated using standard procedures. Since Q–T interval varies with heart rate a corrected Q–T interval (QT_c) was obtained by using the relationship:

$$QT_c = K\sqrt{R - R \text{ interval}},$$

therefore QT_c corresponding to a QT_1 interval

$$= \frac{QT_c \times \sqrt{R_1 - R_1}}{\sqrt{R_0 - R_0}}$$

where QT_0 = observed Q–T interval at equilibration; QT_1 = observed Q–T interval after equilibration; $R_0 - R_0$ = R–R interval in msec at equilibration; and $R_1 - R_1$ = R–R interval in msec after equilibration.

Therefore the real difference in the Q–T interval due to the drug

$$= QT_1 - QT_c.$$

$$\text{Percentage change} = \frac{QT_1 - QT_c}{QT_c} \times 100.$$

We found that at a concentration of 50 µg/ml, amrinone produced no ECG changes except for a sinus tachycardia with a mean increase of 15.64 ± 4.0% ($P < 0.01$). At a concentration of 250 µg/ml the sinus tachycardia was more prominent being 20.86 ± 1.22% ($P < 0.001$). There was also a statistically significant shortening of the Q–T interval ($P < 0.001$).

At 1000 µg/ml, amrinone further increased the heart rate with a mean increase of 45.10 ± 13.26% ($P < 0.001$). There was also greater shortening of the Q–T interval and, occasionally, sagging of S–T segment was noted. Sagging of the S–T segment is a consistent ECG feature following digitalis administration. Dysrhythmic phenomena were seen in all the four hearts treated with amrinone at this concentration. In three of the four hearts, tachydysrhythmia developed, including coupled beats especially of the R on T variety; ventricular premature beats and alternating polymorphic ECG patterns, suggesting multifocal

origin of the ECGs. One interesting finding was that there was no difference in the amplitude of the QRS complex between controls and hearts treated with amrinone at 50 and 250 μg/ml. In contrast, at 1000 μg/ml, the amplitude of the QRS complex was more than doubled (329.3 ± 46.1%) in all the three hearts in which tachydysrhythmia also occurred. The fourth heart developed 2:1 A–V block 45 min after amrinone was added. In that heart, the P–R interval progressively increased prior to the 2:1 A–V block. The heart went in and out of the A–V block but there were occasions lasting several seconds in which P waves were not followed by any ventricular complex and ventricular asystole resulted (Fig. 5). These tachydysrhythmic changes and the A–V block are similar to the ECG changes which are seen in cardiotoxicity due to digitalis.

Because of these interesting findings, the relationship between the changes induced by amrinone on electrical activity of the heart and the mechanics of contractile action of heart muscle was studied. This study was possible because the contractile forces df/dt or dp/dt, were simultaneously recorded and superimposed on the ECG.

In order to elucidate the effect of amrinone on slow Ca^{2+} channel, additional experiments were performed in which verapamil (0.04 μg/ml) was added to the reservoir bottle at the end of the 60 min equilibration period and recirculated. When a new steady state had been reached in about 40 min, amrinone (50, 250 and 1000 μg/ml) was added to the system. In most of the experiments the effects of cumulative dose of amrinone on verapamil-induced changes were studied.

The results of this study have also been published [9]. During peak activity, amrinone

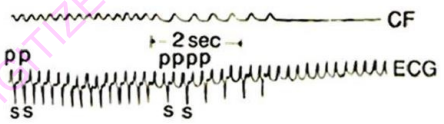

Fig. 5. Guinea-pig Langendorff heart preparation: production of 2:1 A–V block 50 min following the addition of amrinone (1 mg/ml). Ventricular complexes eventually ceased. Upper tracing = contractile force (CF), lower tracing = ECG. (Reproduced from Onuaguluchi, Tanz and McCawley, 1983.)

at 50 μg/ml produced an increase of between 30 and 40% in contractile force when compared with non-treated hearts ($P < 0.01$). In contradistinction, 1000 μg/ml produced, in the three hearts which showed tachydysrhythmia, marked depression of contractile force of over 50% when compared with non-treated hearts ($P < 0.01$). At the intermediate dose level (250 μg/ml), amrinone caused a non-statistically significant 10% increase when compared with control hearts.

When compared with control hearts, amrinone at 1000 μg/ml produced, in the tachydysrhythmic hearts, between 50% and 65% reduction in df/dt ($P < 0.01$). This contrasts sharply with the effect of 50 μg/ml which produced a 20% increase ($P < 0.02$) while 250 μg/ml caused a small and non-statistically significant increase when compared with control hearts.

Figure 6 is a histogram showing the percentage changes in heart rate, cardiac work, MVO_2 and myocardial efficiency from values at equilibration. It shows that 50 μg/ml increased cardiac work by over 40% ($P < 0.01$) when compared with control hearts, 1000 μg/ml caused a depression of nearly 40% ($P < 0.02$) and 250 μg/ml produced a non-statistically significant 25% increase when compared with controls. As regards MVO_2, 50 μg/ml caused an increase of about 50% ($P < 0.02$); 250 μg/ml caused a 75% increase ($P < 0.001$), and 1000 μg/ml induced a 112% increase ($P < 0.001$) when compared with control hearts. There was no difference in myocardial efficiency between control hearts and hearts treated with 50 μg/ml. On the other hand, 250 μg/ml produced about 25% depression ($P < 0.05$) and 1000 μg/ml caused a 75% depression ($P < 0.001$) when compared with control hearts.

In the heart which showed marked elongation of the P–R interval and eventually a 2:1 A–V block, there was marked increase in MVO_2 in spite of a very considerable fall in the contractile force and heart rate. This indicates that such a disproportionate increase in MVO_2 can occur in the absence of tachycardia.

It is clear that amrinone does not have an atractyloside type of action because such an action would result in reduction of MVO_2. It would appear therefore that the fall in the contractile force of the heart which is coupled

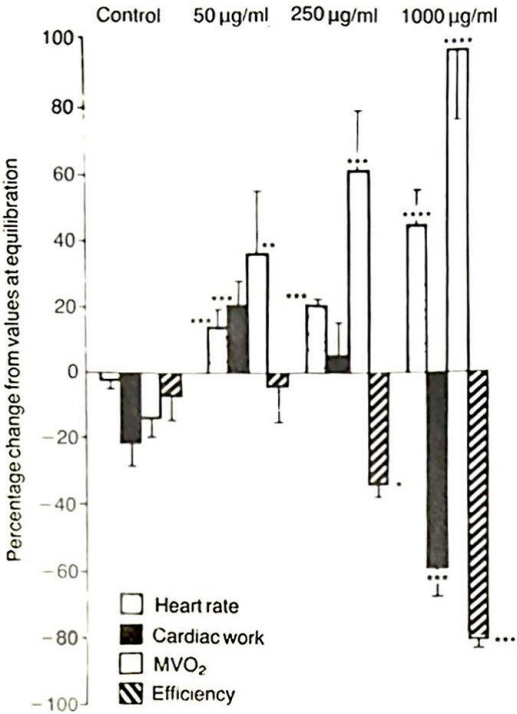

Fig. 6. Histogram showing percentage differences from values at equilibration of values of heart rate, cardiac work, MVO_2, myocardial efficiency, 30 min after equilibration in guinea-pig Langendorff hearts treated with 50, 250, 1000 µg/ml of amrinone and in controls. Number of animals: controls = 7, 50 µg/ml = 6, 250 µg/ml = 4, 1000 µg/ml = 3, Vertical bars = s.e.m., $^{*}P < 0.05$, $^{**}P < 0.02$, $^{***}P < 0.01$, $^{****}P < 0.001$. (Reproduced from Onuaguluchi and Tanz, 1984.)

with excessive oxygen utilization would be attributable to inhibition of coupling of oxidative phosphorylation and not to decreased oxidative process in the heart.

Tanz and Opie [10] also found that after exposure to an arrhythmogenic dose of ouabain in the guinea-pig Langendorff preparation, the considerable fall in cardiac contractile force is often accompanied by a rise in MVO_2. In such situations, cardiac muscle ATP content is markedly reduced [11,12]. Other workers had also shown that while the positive inotropic effect of a non-toxic dose of digitalis is not accompanied by increased MVO_2, toxic doses of digitalis can increase MVO_2 and decrease myocardial levels of ATP and phosphocreatine and thus would seem to uncouple mitochondrial oxidation and phosphorylation [13–15].

Amrinone at 50 and 250 µg/ml, caused dose-related reversal of cardiac depression induced by verapamil. In an earlier study [7] it was shown that the cardiotonic action of amrinone was less marked in Ca^{2+}-deficient medium than in a medium with normal calcium content. It has also been shown that amrinone caused an increase in the calcium transient [16]. These results suggest that the positive inotropic effect of amrinone is at least in part due to Ca^{2+} influx into the sarcoplasm.

We also found that the relaxation of the heart exposed to the highest dose of amrinone (1000 µg/ml) was progressively less complete even before the onset of tachyarrhythmia. The incomplete relaxation during diastole is similar to that which would occur if the perfusate had very high Ca^{2+} concentrations [9].

While there was no difference between control hearts and hearts treated with amrinone (50 and 250 µg/ml) as regards the amplitude of the QRS complexes, the marked depression in the contractile power of the tachydysrhythmic hearts exposed to 1000 µg/ml was accompanied by at least a twofold increase in the amplitude of the QRS complexes. In other words, electromechanical dissociation occurred in hearts treated with tachydysrhythmogenic doses of amrinone [9]. Figure 7 shows the effect of

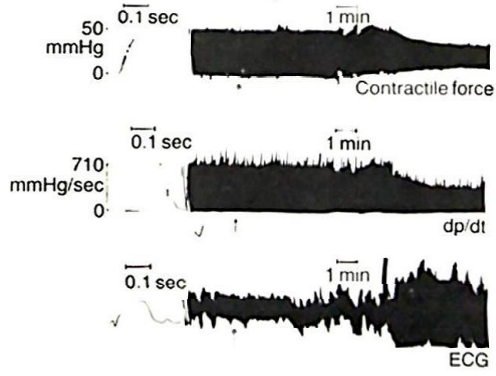

Fig. 7. Guinea-pig Langendorff heart preparation (recirculation system). Effect of 1000 µg/ml of amrinone on contractile force dp/dt, and ECG. Note the inability of the heart to relax fully as myocardial contractility becomes depressed and the voltage of the ECG more than doubled. (Reproduced from Onuaguluchi and Tanz, 1984.)

amrinone (1000 μg/ml) on cardiac contractility and ECG in one of the hearts in which electromechanical dissociation occurred. We suggested that the electromechanical dissociation was due to the rapid influx of Ca^{2+} into the myocardium.

The mitochondria of the mammalian heart have a large capacity for accumulation of Ca^{2+} [17,18]. Influx of Ca^{2+} into the mitochondria should lead to decreased ATP synthesis [18, 19]. Accumulation of Ca^{2+} in the mitochondria has been shown to follow exposure to arrhythmogenic doses of ouabain and our preliminary electronmicroscopical studies seemed to indicate that at the arrhythmogenic concentration, amrinone may also induce the accumulation of Ca^{2+} in the mitochondria. It is likely that rapid accumulation of Ca^{2+} into the mitochondria can damage them and diminish their ability to produce ATP through oxidative phosphorylation. Such damage to mitochondria has been shown to occur in hearts treated with arrhythmogenic doses of ouabain, although they can be prevented by treatment with propranolol [11,12].

Further evidence of myocardial damage is shown by the 17-fold increase over controls in the release of lactic acid dehydrogenase (LDH) from hearts treated with an arrhythmogenic dose of ouabain [10]. Adrenaline, aconitine and very high frequency electrical stimulation also induced increased LDH release when compared with non-treated hearts [10]. In patients with acute myocardial infarction, cardiac glycosides in small doses, augmented creatine phosphokinase (CPK) efflux into the serum [20].

Although calcium currents may be of considerable importance in the genesis of some types of tachydysrhythmia due to amrinone and the cardiac glycosides, there is abundant evidence that other ionic changes are of importance. Indeed we found that substantially increasing the K^+ concentrations of the bathing fluid abolished the automaticity and bigeminy induced by amrinone in the rabbit papillary muscle. Hypokalaemia has also been shown to increase the incidence of digitalis-induced cardiotoxicity [21].

However, it has been shown that toxic doses of ouabain reduce the level of potassium in the myocardial cell [14]. This is related to the inhibition of the Na^+–K^+ ATPase of the sarcolemma [22]. Red blood cell K^+ has also been shown to be reduced by toxic doses of digoxin [23] and it was suggested that red cell K^+ levels should be a sensitive indicator of digoxin toxicity.

One can now summarize the changes in cardiac mechanics, ultrastructure and electrical activity as follows.

1. Amrinone and digitalis at lower serum concentrations have a beneficial positive inotropic action with no impairment of myocardial efficiency. In fact digitalis may improve the efficiency of the cardiac muscle especially if there was sinus tachycardia or atrial fibrillation before treatment with digitalis.
2. At higher serum concentrations, instead of inducing a further increase in contractile force, severe depression of myocardial contractile force and efficiency occurs. Dangerous arrhythmia such as ventricular tachycardia, fibrillation or asystole frequently supervene.
3. The safety margin of digitalis glycoside (i.e. the ratio of the minimum dose producing cardiotoxicity and the dose producing adequate cardiotonic effect) is low: often it is less than 2. The safety margin of amrinone is much higher and has been shown to be not less than 5 [8].
4. At toxic dose levels, mitochondrial damage can be induced by the cardiac glycosides and possibly also by amrinone. Such mitochondrial injury leads to a fall in ATP synthesis and excessive myocardial oxygen consumption (uncoupling of phosphorylation).
5. Damage to the myofibrils also follows toxic doses of digitalis as seen by large increase in LDH and CPK release from the heart exposed to such concentrations and it was suggested [10] that serum LDH estimation might be useful as a clinical guide in diagnosing digitalis overdosage.
6. Increase in Ca^{2+} in the sarcoplasm by whatever mechanism is central to the positive inotropic action of digitalis and amrinone. Paradoxically, excessive increases in the Ca^{2+} content of the sarcoplasm and mitochondria may be primarily responsible for the cardiac depression and fall in myocardial efficiency

induced by digitalis and amrinone at toxic dose levels.

7. Electrophysiological analyses show that shortening of the Q–T interval is constantly observed in the ECG of patients receiving digitalis or amrinone. Digitalis, unlike amrinone, induces prolongation of the refractory period of the A–V node and slows the conduction in the Bundle of His even at non-toxic dose levels. Prolongation of the P–R interval and heart block, sagging of S–T segment and depression of T wave, which are constant ECG features in patients receiving digitalis, have not been observed in patients receiving amrinone but our work on isolated heart preparations shows that these features can be induced by amrinone at toxic dose levels.
8. The possible role of Ca^{2+} currents in the genesis of some ECG abnormalities have been highlighted. However, hypokalaemia causes the heart exposed to digitalis and amrinone to be more prone to developing arrhythmia.
9. It is now certain that inhibition of the Na^+–K^+ ATPase by digitalis would cause a diminution in the K^+ content of the myocardial cell which in turn would contribute to the genesis of some forms of arrhythmia. Red blood cell Na^+–K^+ ATPase is also inhibited and estimation of red cell K^+ content should be a sensitive indicator of digitalis overdosage.
10. On coronary vessels, digitalis causes vasoconstriction while amrinone induces vasodilatation. Mild vasodilatation of peripheral arteries is also produced by amrinone.

We can now look at the haemodynamic effects of digitalis. However, in order to comprehend how these changes come about, we must understand certain basic principles in haemodynamics and the mechanics of heart muscle activity.

The first of these principles deals with the *Determinants of* MVO_2. The most important are: heart rate; intramural tension (which increases as the aortic impedance or the ventricular volume increases); and myocardial contractility. MVO_2 varies directly with the values of these determinants.

The next is the *Law of Laplace* which states that, at equilibration, the distending pressure (P) in a distensible hollow object is equal to the tension in the wall or intramural tension (T) divided by the principal radii of curvature of the object (R_1 and R_2). If the object is spherical then $R_1 = R_2$ and therefore $P = 2T/R$ or $T = PR/2$.

Thus, for any given pressure developed by the ventricle, the intramural pressure (which is responsible for a portion of the MVO_2 but does not contribute to the ejection pressure of the ventricles) increases as the diameter of the hearts increases.

The next is *Poiseuille's Law* which looks at the relationship between the flow in a long narrow tube, the viscosity of the fluid, the radius of the tube and the pressure head responsible for the flow. It states that the flow varies directly with the pressure head but more importantly with the fourth power of the radius of the tube. Thus, the resistance to flow varies inversely with the fourth power of the radius. Therefore, very small changes in the calibre of the vessels lead to marked changes in the flow. Thus an increase of only 19% in the radius of the vessel causes the flow to be doubled and when the radius is doubled the resistance is reduced to 6% of its previous value [25].

Digitalis, because of its positive inotropic effect, will cause increased ventricular emptying leading to a fall in left ventricular end-systolic and end-diastolic pressures and thus to a fall in ventricular volume, and by the Law of Laplace, to a reduction in ventricular intramural tension. This, in addition to the reduction in heart rate, would lead to appreciable reduction in MVO_2 and an improvement in the efficiency of the heart.

It must be stated that although in the normal subject digitalis causes generalized vasoconstriction with an increase in peripheral arterial resistance, the opposite effect results in patients with severe heart failure. This reduction in peripheral vascular resistance is not due to a direct effect of digitalis but to a reduction in the high sympathetic tone seen in heart failure. The sympathetic tone falls because of the improved cardiac output occasioned by digitalis [22]. However, digitalis does not cause an increase in coronary artery blood flow and indeed its vasoconstrictive effect may lead to worsening of myocardial hypoxia, thus increasing the

chances of the heart developing arrhythmias.

Amrinone, which is much more easily washed out from the heart than digoxin, causes appreciable direct peripheral vasodilatation [26,27] and induces very marked coronary vasodilatation [6,7], has a much greater safety margin than digitalis and shoud have replaced digitalis in the treatment of chronic congestive heart failure but for the one report of thrombocytopoenia in some patients receiving amrinone [28].

From what has been said so far, one can easily infer that probably the best way of increasing cardiac output is by reducing aortic impedance which would in turn reduce ventricular volume and thus intramural tension without inducing the excessive Ca^{2+} influx into the myocardium which could follow the administration of cardiotonic drugs, and which could be responsible for a number of cardiotoxic effects of digitalis and amrinone, such as paradoxical reduction in cardiac output and dangerous arrhythmias.

It is surpring therefore, that in spite of our profound knowledge of haemodynamics, no one had seriously considered, until the late 1970s, the use of vasodilators in the treatment of chronic congestive heart failure. However, with the success of vasodilators, for example: sodium nitroprusside [29]; phentolamine [30,31]; glyceryl trinitrate [24,32]; and dopamine [33,34] in the management of some types of acute myocardial failure caused by acute myocardial infarction, and the availability of many relatively safe oral vasodilators, the use of vasodilators in the treatment of chronic congestive heart failure is now seriously considered.

The vasodilators which have been used [24,35–38] include: organic nitrates (glyceryl trinitrate and isosorbide dinitrate); hydralazine; the quinazoline vasodilators (prazosin and trimazosin); minoxidil; and more recently, angiotensin I-converting enzyme inhibitor, captopril [39,40]; and calcium antagonists, especially nifedipine [41].

Combination therapy with a vasodilator (nitroglycerine or isosorbide dinitrate) and an arteriolar dilator, e.g. hydralazine or prazosin produces better results than the single drug therapy [42]. As prazosin and trimazosin relax both venous and arteriolar smooth muscles, they are probably more effective than the others if single drug therapy is embarked upon.

Although improvements in patients' general condition have been demonstrated, no improvement in maximal exercise capacity was observed in patients with Class II and III chronic congestive heart failure receiving combinations of hydralazine–isosorbide dinitrate vasodilator therapy [43]. However, prazosin improved exercise tolerance in patients with chronic refractory heart failure [36].

Although the salutary effect of prazosin and trimazosin are not affected by the age of the patient, diabetic state, or even by the cause of the congestive myocardiopathy, the best haemodynamic response, as would be expected, occurs in patients with the most severe haemodynamic derangement [37]. There is, however, some evidence that tolerance to prazosin may develop rapidly [44]. Tolerance to the organic nitrates and hydralazine has, however, not been observed [45].

Even a bed of roses has some thorns and so it should not be surprising that vasodilator therapy of chronic congestive heart failure would have some problems. The first is that most of the non-specific vasodilators produce a number of adverse effects including increased salt and water retention and reflex tachycardia. Hydralazine, in addition, can induce lupus erythematosus syndrome, leucopoenia and peripheral neuropathy. Captopril can induce nephropathy with proteinuria, leucopoenia, and drug rash.

Another problem concerns the criteria for selection of the type of vasodilator therapy. However, in discussing this issue, Mason stated that selection of the appropriate vasodilator is predicated on the patients' predominant refractory haemodynamic abnormalities and symptomatic manifestations. He was of the opinion that chronic long acting nitrates are indicated when the principal difficulties are dyspnoea and increased left ventricular filling pressure; hydralazine is indicated when low cardiac output and fatigue predominate; prazosin, hydralazine-nitrates or hydralazine–prazosin would be indicated when excessive pre-load (right atrial pressure) and dyspnoea in conjunction with depressed cardiac output and fatigue are the predominant manifestations [22].

In the words of Zelis *et al.*, 'the concept of vasodilator therapy is very simple; if the sick

heart works less, it should get better' [45]. An Editorial in the *Lancet* in 1979 [46] under the title 'Treatments for heart failure: stimulation or unloading' concluded that the best treatment would be to reduce the load on the heart. I believe that I have shown that vasodilator therapy should be preferred to digitalis in the management of many cases of chronic congestive heart failure. In any case, digitalis has been found not to be effective in congestive heart failure due to cor pulmonale, hypertrophic cardiomyopathy, heart disease from coronary artery disease, and mitral stenosis without atrial fibrillation.

I have also shown that amrinone, which has a positive inotropic effect like digitalis, but unlike digitalis produces vasodilatation of the systemic and pulmonary vascular beds and marked coronary vasodilatation, should also be preferred to digitalis, especially as it has a much wider safety margin and at normal therapeutic dose levels produces hardly any cardiotoxic effects or ECG changes except some slight shortening of the Q–T interval.

I think we need to look for newer compounds with an amrinone type of action and indeed we need to compare the long-term effects of amrinone or amrinone-type drugs with those of prazosin alone or in combination with hydralazine or nitrates in patients with various types of chronic congestive heart failure. It seems to me that unless the long-acting oral vasodilators have serious adverse effects or tolerance to them develops often, and unless the thrombocytopoenia induced by amrinone is found to be a major problem, the days of digitalis glycosides as first-line drugs in the management of chronic congestive heart failure, may be numbered.

Finally, I thank you all for listening very patiently. I must again say that it is a great honour to be asked to give this lecture and I hope that in spite of my inadequacies I have managed to do justice to the pre-eminent role of digitalis during the past two centuries in the management of chronic congestive heart failure — and to bestow honour to this great physician: a man who was the best graduating student of his class at Edinburgh University and who did not need to look for a career in academic medicine outside the U.K. but who, probably because he had in him the undying spirit of the early Scottish explorers of Africa, came to start the first university-sponsored medical school in British West Africa. And what a fine job he did. It is certain that many of us here today owe a lot to Alex Brown. I am confident that the life of this great physician and medical educator will continue to be a shining example and a beacon of light to guide all those who come to teach or study at this medical school.

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