This edition of chronicles of medical history in Africa will focus on the first published report of malaria by Alphous levaran in 1880. Before extolling this great contribution to medical knowledge let us examine briefly the proper place and role of history, arts and humanities in the development of human societies.

Science has a long and interesting history. Sadly the medical scientist has little time for history and the historian knows little of medical science. History, Arts and humanities make learning smoother and more pleasant than when the hard facts are studied in isolation. The arts and humanities have long been associated with great men of science. Girolamo Frabcastro was a physician who made important contributions to our knowledge of contagion and contagious diseases. He was also a humanist who wrote poetry and whose range of interests was extraordinarily wide. Paracelsus was also a physician who wrote theological and philosophical works. Here at the University College Hospital, Dr Kunle George (dermatologist) has written great books of poetry. At the level of great genius the boundary between science and the arts and humanities is blurred and the soul of the gifted is restive with ideas from every field of human endeavour.

Albrecht von Haller (1708-1777, Swiss physician, botanist, and poet, considered one of the greatest modern physiologists), entered the literary scene with a volume of poems which exerted a very strong influence on German literature and in some ways even anticipated Goethe. Besides writing enormous works of students and colleagues and writing innumerable letters on scientific subjects, Haller also wrote three novels and several theological books. The great French philosophers of the period of enlightenment- men like Diderot, d’Alembert, Rousseau, Voltaire- were philosophers, poets, historians and were all keenly interested in science.

All through history our thoughts have been shaped by great insights into human nature that are first and primarily supernatural revelations, beliefs, interpretations of dreams and visions, prophetic messages and convictions of the soul. Great leaps in faith, if I may use the right words, have propelled science and medicine. This intangible aspect of man’s nature has in many instances been expressed in poems and in one or another kind “religious” prose. They gave birth to civilizations and science, and continue to direct man’s moral perspective. These thoughts that are initially intangible have laid down the structure and the infrastructure of almost every area of man’s existence. It is the origin of science as we know it today, and will continue to be so. While we focus on the great achievements of men and the infrastructure of medicine, we must bring to remembrance the origin of these things that seem to confer a kind of pseudo feeling of human power and control over natural, and as it is turning out, supernatural events. The origin of thought and emotions will remain central to leaps in the progress of humanity, and will continue to remain so.

I need to make a statement here that the proper interpretation of the people and great events in history, events that will be the main theme of the chronicles of medical history in Africa, will depend on complete and proper appreciation of the origins. That even while we can identify the people and moments of medical or any kind of history, we need to know that true discovery has always come from human reasoning and that these discoveries have more often than not led to the imprisonment of human mind in some cases. The case of Charles Darwin easily comes to mind. The idea of evolution of species has been adopted by many as true. As a scientist I wish to say that the evolution of species is a fact proven by evidence in every area of biology, however, the insight that resulted in that great revelation remains supernatural. This initial insight on the nature of evolution has been remodeled into a theory that removes the origin of the idea from its perspective. Albert Einstein could not tell exactly where the theories of relativity and the photo electric effect came from, but they fit nature perfectly and wonderfully. Today we have elaborate formulae explaining these processes and very delicate equipment used in detecting them. The power that these sciences give to man is very enormous; science gives us control and history happens every day. But who can say where the next great discovery will come from? Who can say where the origin of the discovery lies? Where do discoveries come from and why?

I can say this; the next great discovery will come from a revelation and a whole lot of science will develop after it. This power and complexity that keeps growing with every leap in human thought has in many instances ensnared the followers and disciples of science who may not be aware of or choose to ignore the origin of thought. They are held in a maze of a belief that
the human brain is the all in all, that there is really no supernatural. Is this really the truth? In the midst of growing doubts of our place in the universe, of reductive thinking and mechanistic explanations of phenomena, another “mysterious” revelation breaks forth from a “prepared mind” that moves science yet again into more complexity, beauty and more power for man. Sadly there also comes with this more doubt, confusion, fears, and disillusionment. People want to see things not only believe. Yet in this confusion a few have found the origin and have stayed with it. The truly great thinkers are fixed and sure of the origin of thought and they remain believers of the origin. They believe before they see. The great teacher is the one who has found this path to true knowledge and who has the ability to point others to this road of really great discoveries, to the road that leaves exciting history behind. History is to guide us not to bind, blind or lead us.

Reasoning is the most superior form of thought, of science, art, religion, humanities, and every social interaction of man. But we must learn to reason right. This is where every human-based structure seems to have failed. It seems the ability to reason right is beyond the power of man. This ability is available to all those who truly seek it, those who are not carried away by the great methods and discoveries of science or medicine or the history of such things as they are. They love and appreciate history for what it is, a source of motivation and strength to face and discover the future. The source remains supernatural.

I love biology and have esteemed her above the other sciences but for mathematics; however, I have esteemed the origin of great and true thought (reasoning) above every other knowledge in this universe. There is absolutely no doubt; this knowledge originates from the Divine and that is where we must direct our focus. Knowledge is secondary to the origin of human thought. Thought and consciousness give birth to all our experiences. Let this be clear even as we celebrate great moments and great men of science and medicine. I will leave this here because the explanation of the origin of human thought is beyond the scope of this exposition. We shall return to malaria, a disease that has shaped human history more than any other disease until the recent HIV-AIDS pandemic.

The history of malaria predates humanity, as this ancient disease evolved before humans did. Malaria, a widespread and potentially lethal infectious disease, has afflicted people for much of human history and has affected settlement patterns. It has also been said that malaria originated from Africa but the earliest recorded writing on the disease was by a French physician. The causal relationship of pigments to the parasite was established in 1880, when the French physician Charles Louis Alphonse Laveran, working in the military hospital of Constantine Algeria, observed pigmented parasites inside the red blood cells of people suffering from malaria. Many others had seen various objects in the peripheral blood of malaria patients – Meckel (1847), Furichs (1858), Planer (1854), Delafield (1872), and Jones (1876) – yet none developed their observations in a systematic manner, Laveran’s first communication appeared in the Bulletin de L’Academie de Medecine, 19: 1235-1236, 1880. He witnessed the events of exflagellation and became convinced that the moving flagellae were parasitic microorganisms. He called this microscopic organism Oscillaria malariae and proposed that malaria was caused by this protozoan. Like many other notables in the history of tropical medicine, Laveran first became acquainted with the problems he was to study throughout his life during his career as a military surgeon. He was born in Paris, the son and the grandson of physician, and was awarded his degree in medicine by the University of Strasbourg in 1867. After several military assignments in France, he was transferred in 1878 to Algeria, where he became deeply interested in malaria, the cause of which was then being widely discussed. During a series of microscopic blood examinations of malaria patients in Constantine, he discovered spherical pigmented bodies with ameboid movement which he had until then confused with pigmented leukocytes. This was the third time that microorganisms had been found in human blood, the first two being the causative agents of relapsing fever and anthrax. When Laveran’s discovery was confirmed, the Academy of Sciences in Paris elected him to honorary membership service. In 1904, Laveran retired from military service and joined the Pasteur Institute, where he devoted himself entirely to bacteriology and parasitologic research. He published more than 600 scientific papers dealing with malaria and many other tropical diseases. Up to this day malaria remains a major public health problem, causing 250 million cases of fever and approximately one million deaths annually. Understanding its history is important for the proper appreciation and evaluation of the disease. Laveran was awarded the 1907 Nobel Prize for Physiology or Medicine “in recognition of his work on the role played by protozoa in causing diseases”. Reproduced on the next page is the article in full with a single plate. This article marked a great moment of medical history. It started and took place in Africa.
A NEWLY DISCOVERED PARASITE IN THE BLOOD OF PATIENTS SUFFERING FROM MALARIA PARASITIC ETIOLOGY OF ATTACKS OF MALARIA.

Charles Louis Alphonse Laveran (1845-1922)


On 20 October of this year, while I was examining microscopically the blood of a patient suffering from malaria, I noticed, among the red corpuscles, elements that seemed to me to be parasites. Since then, I have examined the blood of 44 malaria patients; in 26 cases, these same elements were present. This convinced me of their parasitic nature. These elements were not found in the blood of patients who were not ill with malaria. I will describe these elements as No. 1, No. 2, and No. 3. Eventually, it will become evident that this nomenclature is useful as it makes no assumptions as to the nature of the parasites.

1. Description of Parasitic Elements Found in the Blood

No. 1 – These are elongated bodies, with ends more or less tapered, often crescent-shaped (see Plate 5, Figs. 3 and 4), but sometimes ovoid (Fig. 5). In length, they measure from 8 to 9 microns and in breadth, they average 3 microns. A very fine line indicates the contour while the body itself is transparent and colorless at the periphery; toward the central part, there is a dark stain due to a series of rounded granulations that are probably pigment granules. Exceptionally, this stain is situated at the periphery. The granulations are often symmetrically disposed, in a crownlike arrangement, similar to the one I shall describe for No. 2. On the concave side of the crescent-shaped bodies, a curved pale line often seems to connect both ends of the crescent. This line is shown on Fig. 4. No. 1 bodies seem motionless; when their outline changes, it does so very slowly.

No. 2 – These bodies present different shapes that vary with their being in states of rest or motion. In states of rest, the body is generally round and transparent, finely contoured, measuring 6 microns in diameter. Inside the body (Fig. 6), round pigmented granules of equal size are usually quite regularly arranged in a ring; one might say they look like a necklace of black pearls. In motion, one sees very transparent filaments that are rapidly moving in all directions. These movements may be compared to those of nematodes that would have one end attached to the inside of the spherical part. These filaments set the neighboring red blood corpuscles into motion, and this is easily observed. The length of the filaments or mobile appendices is approximately three or four times the diameter of the red corpuscle. I had the impression that three or four of these filaments surround every so-called No. 2 body, but there may be more of them, since only perfectly focused mobile filaments are perceived. These mobile filaments are sometimes regularly spread out on all sides (Fig. 7) or all are sometimes clustered on one side (Fig. 8). The free ends of the moving filaments are swollen, as is indicated on Fig. 7.

While these filaments or motile appendices move around freely, the spherical body on which they seem to be inserted oscillates more or less rapidly and even seems, at times, to move about so that all its parts follow the same direction. The pigmented granules move around freely inside the body and assume various configurations.

No. 2 bodies very often later their shapes while one observes them. They become longer, flatten out, and become spherical again. In this last instance, the movements recall those of amoebae. Several times, it happened that while I was observing the motion of No. 2 bodies one of the mobile filaments would leave the round body and continue to move around the red corpuscles. Fig. 9 shows one of these filaments that has become free.

In several instances I have also observed in the slides of malaria patients, apart from the elements heretofore described, rounded bodies larger than the No. 2 bodies and usually even larger than leukocytes, which had inside them moving pigmented granulations. These bodies contained no mobile filaments and their motion was Brownian-like (Fig. 10).

No. 3 – These bodies are round, larger in diameter (8 to 10 microns and sometimes greater), than No. 2 bodies, slightly granular, motionless, without any apparent peripheral filaments. Inside the bodies one sees pigmented granules sometimes arranged like those in No. 2 (Fig. 11) but more often disposed haphazardly and in variable numbers. These bodies alter in shape...
increasingly and so tend to become very different from
the type I just described (Fig. 12 and Fig. 13).

In addition to No. 1, 2, and 3 bodies, one nearly always
finds small, rounded, mobile, and bright bodies and
crimson red or light blue pigment granules. These
pigmented granules are free or are included in No. 3
bodies or in leukocytes. The crimson red pigment seems
to undergo transformation, and the result would seem
to be the blue pigment.

II. Refutation of Some Objections. Methods of Blood
Examination
Before I delve into the nature of the parasitic elements
and their pathologic role, I wish to answer two
objections made to me several times which probably
will be presented to me again:

(1) Were the above-described parasitic elements
really found in the blood of the patients? Were they
not accidentally introduced into the slides?

(2) Were altered blood elements mistaken for
parasitic elements?

The technique I used in all my preparations should
shield me from the first of these objections. The glass
slides were carefully washed in alcohol; the patient's
finger was swabbed with alcohol; pure blood was
examined without the addition of another fluid; and
finally the slides were sealed with paraffin. It is true
that all these precautions would not prevent floating
air particles from entering the preparations, but how
could one possibly maintain that the complicated
parasites I have described were floating in the air only
while I was examining the blood of malaria patients?
How could one correlate the relationship I have many
times ascertained between the abundance or rarity of
parasites and the degree of sickness or apparent
recovery of malaria patients if the inclusion of the
parasites was due only to chance? Moreover, I was
always careful to prepare the slides in different locations
in the wards or in my laboratory, and the results were
identical. I beg to dispose of this objection and to
maintain that the parasites were truly in the blood of
patients.

The second point seems even easier to deal with than
the first. It is impossible to confuse No. 2 bodies
equipped with mobile filaments with any possible
normal or pathologic element of the blood. The swift
movements of the filaments have nothing in common
with the slow motions of leukocytes, and the
pigmented granules, mobile or arranged in a ring,
should not be confused with the granulation of
leukocytes. All my colleagues to whom I was able to
show these No. 2 bodies in motion did not hesitate
for a single second in recognizing that what was moving
was indeed a parasite. One would only need a glance
at Figs. 7 and 8 to become convinced that such bodies
cannot be confused with leukocytes, however altered
these may be. Even when they are motionless, No. 2
bodies resemble leukocytes only vaguely. They are
usually smaller, the granulations are dark or crimson
red and arranged in a ring, and they have no inner
nuclei.

It would be just as impossible to confuse No. 1 bodies
with blood elements. Erythrocytes, sometimes similar
in shape to the bodies, never have any internal
pigmented granules. It is true that No. 3 bodies look
very much like pigmented leukocyte. They are alike in
shape and measurements. Yet, the differences are great.
Pigmented granules have a regular arrangement in No.
3 bodies (Fig. 11); there are no internal nuclei, and these
elements do not take carmine dye as do leukocytes.
Moreover, it is easy to ascertain that No. 3 bodies are
the result of transformation of No. 2 bodies, the living
nature of which is incontestable.

III. Nature and Pathologic Role Played By Parasitic Elements
Found in the Blood
Bodies No. 1, 2 and 3 seem to represent different
aspects or different phases of the evolution of the
same parasite. It is evident that No. 3 bodies are the
result of a transformation of No. 2 bodies after their
death. It is easy to convince oneself in the following
fashion. One looks for a No. 2 body with mobile
filaments and after having found one that is
caracteristics and very lively, the slide is paced on the
microscope and is observed from time to time. After
a variable period (from some minutes to several hours),
the movements cease and the filaments become
invisible. The body changes from its Fig. 7 or 8 aspects
to the one shown in Fig. 6. After a while, No. 2 body
enlarges as if flattening out while the pigmented
granules disassociate, forming a widening circle (Fig.
11). Finally the parasitic organism alters its shape to
the point where it is no longer recognizable. The
pigmented granules become arranged irregularly. They
accumulate at one point or disappear altogether with
the exception of one or two. The same procedure,
when applied to No. 1 bodies, gives similar results.
The bodies become shapeless after a while, although
not so rapidly as No. 2 bodies. No. 1 bodies become
first ovoid and then spherical and irregular.

Often, one finds in the slides ovoid bodies that appear
to be intermediate between No. 1 and No. 2 bodies.
Nevertheless, I have never witnessed a No. 1 body
transforming itself into No. 2 body even after a 36-
or 48-hour period of observation.
Mobile No. 2 bodies are mostly found in the blood of patients who have suffered a recurrence of fever and who do not take quinine sulfate regularly.

Plate 5. Key to drawings. Fig. 1. Blood red corpuscle Fig. 2. Polymorphonuclear leukocyte. (These elements serve as point of comparison to give an idea of the measurements of the other elements; all diameters magnified [greatly].) Figs. 3 and 4. No. 1 bodies. Fig. 5. Ovoid intermediate body between No. 1 and No. 2 bodies. Fig. 6. No. 2 body, motionless. Fig. 7. No. 2 body with mobile peripheral filaments bulging at the free end. Fig. 8. No. 2 body with mobile filaments grouped laterally. Fig. 9. Mobile filaments freed from the body. Fig. 10. Spherical body filled with mobile pigmented granules. Fig. 11. No. 3 body. Figs. 12 and 13. Distorted No. 3 body. Fig. 14. Pigmented elements from the blood of a man who died of pernicious fever; (a, a’) elements similar to No. 1 body; (b’, b’, b”) elements similar to No. 3 bodies. Fig. 15. Elements from the spleen of a man who died of pernicious fever; elements similar to No. 3 bodies.

The very fact that the parasitic organisms above described are found in an alkaline medium such as blood leads one to think that the parasites are of animal and not vegetable origin. The rapid and very varied movements of the filaments of No.2 bodies, as well as the modifications of form they go through, lead the researcher to think of an organism an infusoria. Is it as I first thought, an amoeba, or could bodies No.1 and No.2 be the result of an agglutination of cystlike parasites formed by normal elements in the blood? Could these parasites, fully developed, be the mobile filaments of No.2 bodies that sometimes leave the bodies to lead independent lives? This last hypothesis seems to me the most probable one. Once free, the mobile filaments are very much like filariae; and several researchers, Hallier among them, think filariae play an important part in the pathology of swamp fevers. The small, mobile, bright bodies, almost always present in the preparations, may be the first phase of these little bodies attaches itself to a red corpuscle and makes the effort, if I may say so, to penetrate into the interior. The important role played by the parasites above described in the pathogenesis of swamp fevers may be evaluated as follows:

1. These parasites are found only in the blood of patients suffering from malaria. It is fair to add that they are not always found there but, since only one or two drops of blood are examined, it is obvious that when the parasites are very scarce, their presence is difficult to establish.

2. These parasites, while abundant in the blood of patients who have suffered from the fever for some time and who received no regular treatment, vanish from the blood of those treated for a long time with quinine sulfate, and who may be considered cured. Many of the patients I examined had received quinine sulfate for several days, and that could explain the high percentage of negative results I obtained.

3. In the blood of patients who have died of pernicious fever, one finds a great number of pigmented elements that look very much like No.3 bodies or, in rarer instances, No.1 bodies. The presence of these elements in capillaries of all tissues and of all organs, particularly of the spleen and liver, is characteristic of acute malarial infection. Fig. 14 shows pigmented bodies found in the blood of a man who died of pernicious fever, and Fig. 15, similar bodies found in spleen tissue in another case of pernicious fever. The resemblance of these bodies to those I described as No.1 bodies and No.3 bodies, and who parasitic nature I believe to have established, is striking. From where come these parasitic elements found in the blood of malaria patients? How do they get into the human system? How do they cause intermittent fever and other signs of malaria? Only now is one able to pose these important questions.

CONCLUSION
Parasitic elements are found in the blood of patients who are ill with malaria. Up to now, these elements were thought incorrectly to be pigmented leukocytes. The presence of these parasites in the blood probably is the principal cause of malaria.
Gastrointestinal Stromal Tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract. They are rare tumours, comprising 1% of all GI malignancies. They represent approximately 5% of all soft tissue sarcomas. Majority of these tumours arise from cells that are not clearly of smooth muscle or neurogenic origin. They are slow growing, indolent tumours. Over the past few years the term gastrointestinal stromal tumours (GISTs) has been introduced to classify mesenchymal tumours arising in the luminal tract. They are usually extraluminal in origin, but may ulcerate through the overlying mucosa. Virtually all GISTs have gain – of – function c – kit mutation (a protooncogene growth factor receptor). The objective of this case report is to sensitize clinicians to the possibility of GIST in patients presenting with dyspepsia.

Case report
A 49 year-old man who presented with recurrent upper abdominal pain of 9 years, and 6 months history of right hypochondrial swelling and weight loss. He also had history of early satiety and vomiting. No history suggestive of upper gastrointestinal bleeding. Clinical examination revealed wasting, pallor and ankle oedema.

He had hepatomegaly which was firm, irregular and tender. Succussion splash was positive. An impression of gastric outlet obstruction secondary to antral carcinoma to rule out carcinoma head of pancreas with hepatic metastasis was made.

Abdominal ultrasound scan revealed hepatomegaly and a mass distal to the stomach.

Peripheral blood film examination revealed iron deficiency anaemia and thrombocytosis, while serum chemistry showed hypoalbuminaemia.

An upper gastrointestinal endoscopy revealed a mass in the second part of the duodenum which was ulcerating and vascular. Multiple biopsies were taken for histopathology. The tissue was sectioned and stained with haematoxylin and eosin. It showed spindle shaped cells containing large nuclei with blunt edges and were surrounded with mild to moderate cytoplasm. There is loss of overlying mucosa. Features are in keeping with gastrointestinal stromal tumour.

Exploratory laparotomy revealed a mobile mass in the 2nd and 3rd parts of the duodenum which was firm-hard, irregular, measuring about 12cm in diameter. There were metastases to the liver and paraaortic lymph nodes. He had gastrojejunostomy and paraaortic lymph node biopsy for histology which also revealed a metastatic gastrointestinal stromal tumour.

Postoperatively, patient was stable and he was discharged home 11 days after. He is presently stable and on follow up. He has been commenced on cyclical cytotoxic chemotherapy using 5-fluorouracil.

DISCUSSION
Gastrointestinal Stromal Tumours (GISTs) are slow growing and as such are usually asymptomatic until they become quite large. About 30% of GISTs are detected during investigations for unrelated disease. The typical age at presentation is over 40 years {median age is 50-60 years} and there is male predominance. Symptoms at presentation include gastrointestinal...
bleeding, dyspepsia, and with large tumours, obstructive symptoms. In this case report, our patient presented with dyspeptic and obstructive symptoms. His peripheral blood film also revealed iron deficiency anaemia, probably due to occult gastrointestinal bleeding. Our patient is within the usual age of presentation. GISTs can spread into regional lymph nodes, liver, lung and peritoneum. Our patient had metastases to the paraaortic lymph nodes and the liver. The initial diagnosis of GISTs is best made at the time of endoscopy. Probably, if our patient had presented earlier and had upper GI endoscopy, the diagnosis could have been made before he reached this advanced stage.

The most common affected site is the stomach in about 70% of cases followed by the small intestine (25-40%). The colon, rectum and oesophagus are less affected. In our patient the tumour was found in the second part of the duodenum. It was well circumscribed with distinct margins and surrounded the papilla. In a study conducted in Pakistan, 20% of 205 leiomyosarcomas were abdominal.

GISTs are most common in the jejunum, least common in the duodenum. Until 1981, 123 cases of duodenal GISTs were reported in a review of literature. The endoscopic appearance varies depending on the size of the tumour and whether it is intraluminal, intramural or exoenteric. The tumour may be submucosal and develop a central ulceration as it enlarges. The ulcerated form would presumably be the most common, since bleeding is the chief complaint in over half of the cases. In this case presentation the tumour was intraluminal and ulcerated, although there was no evidence of upper GI bleeding. The chief complaint in our patient was upper abdominal pain.

Endoscopic ultrasound (EUS) is also helpful in determining the depth of invasion as well as regional lymph node involvement. Although, our patient did not have EUS done, regional lymph node involvement was revealed at laparotomy.

Immunohistochemical analysis is used for confirmation of diagnosis C-kit (CD117) and CD 34 have significant importance in identifying GISTs as these tumours have a strong affinity for the respective antibodies. These tumours also show immunopositivity for smooth muscle actin (SMA) and S-100 protein. In our patient the diagnosis was reached by a combination of clinical presentation, endoscopic appearance and histology.

The most useful clinical predictor of outcome is the mitotic index of the tumour. Those with a mitotic rate of greater than 2 per 10 high-power fields have a much higher risk for recurrence or metastases. The size of the tumour is also a clinical predictor of outcome, with those larger than 5 cm at higher risk of metastases. GISTs of less than 2 cm with negligible mitotic activity are considered very low risk, they may still metastasize. Our patient had an extensive tumour, greater than 5 cm and hence metastases to the liver and paraaortic lymph nodes.

Surgery is the treatment of choice. Some advocate use of adjunctive radiation and chemotherapy. Recently, the tyrosine kinase inhibitor imatinib mesylate (ST 157, Gleevec) has been used successfully in a metastatic GIST. Monitoring the patient long after resection is necessary as the tumour has a tendency to recur. Our patient was offered imatinib, but could not afford it because of cost, hence the choice of fluorouracil.

CONCLUSION
GIST of the duodenum is an uncommon cause of gastric outlet obstruction. Our patient presented late with attending poor prognosis. The use of cytotoxic chemotherapy has not been found to be of proven efficacy. The cost of imatinib has placed it out of reach of use for patients in our environment.

REFERENCES
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Good afternoon, Our Chief Medical Director, Chairman Medical Advisory Committee, Our Premier E-I-C, Our Editorial Consultant in absentia, other members of the advisory board, board alumni here present, The President, Association of Resident Doctors (ARD) and all other executives here present, noble members of the Editorial Board of Annals of Ibadan Postgraduate Medicine (AIPM), other doctors here present, ladies and gentlemen.

It gives me pleasure and a whole sense of deep humility in welcoming you all to this august occasion of commissioning of the office of the AIPM.

This occasion is a milestone in the life of our dear Journal as a product and of the Board as a people. It will not be out of place therefore in trying to get down the memory lane depicting the genesis of the edifice we are commissioning today.

THE DREAM
The conception of the AIPM was primarily borne out of the concern that most resident doctors in the country did not attach adequate importance to research and publications during their training as residents. This observation provokes the desire in 1999 to create a medium that would arouse this publication consciousness and allow for dissemination of scientific findings and information. The aim of which is to groom resident doctors in the act of scientific writings and publications.

The burden that evolved then fell in our premier EIC who had to spear head not only the conception but the birth and the continuous nurturing of this idea – AIPM Journal. He has never faltered on this noble cause and for this we are celebrating him today.

THE REALITY
It is the saying of the elders that “The wisdom of sustaining a home is far more than that to build it”. It is to the glory of God that the dream of AIPM in 1999 become a reality in 2003 with the publication of the first edition then (Vol.1, No.1, November 2003). This was actually launched on the 12th of December 2003, (exactly 5yrs ago). The template that produce this journal was made up of erudite member of like minds including Dr. W. Balogun, Dr. M. Kuti, Dr. A. Dada, Dr. O.A. Ayinde, Dr C. Eyo, Dr U. O. Eze, Dr O. Omisanjo, Dr O. E. Amoran and Dr I. Oluwayemi. Professor S Kadiri has been and is still our Editorial Consultant.

Articles presented are of national importance and academic relevance. Since this first edition, the Board has not looked back and always strive to meet her biannual publication schedule.

THE ACHIEVEMENTS
Since the inception of the Board and the Journal, we’ve maintain a consistency in publication schedule. This has not only promote our publishers (ARD) image alone but that of our Noble Premier Institution - the University College Hospital, Ibadan as an entity.

Within the period of existence, we’ve been able to:
- get indexed on African Journal Online
- indexed on African Indexed Medicus
- organized in-house seminar for Board members on the art of scientific writings and publications in May 2007.
- Develop and operate our own website: www.aipm.org.ng linked to our indexed portals. This has increased our visibility as well as our authorship
- Secure our Operation office, which we are commissioning today
- Securing intercom facilities recently.

No tree can make a forest, our humble achievements can never be complete without mentioning the role which our Management and publishers has performed towards making the Board and Journal a reality out of a dream.

THE CHALLENGES
The challenges of a scientific publication could be numerous – article contribution for publications, reviewers busy schedules, correspondences etc. However, due to quality of our journal, I’m happy to say that we are now receiving article from India and Europe.

The major constraints to the Board this year is mainly finance from our publisher which really held us back in meeting our statutory objectives, its our hope that the incoming executive will overcome this problem. We are hereby soliciting for the management support in this direction.

PROSPECT/PROJECTION
The newly included Board came to office in August this year and with the aforementioned challenges with renew vigour strategize to overcome this by:
- strengthening the financial base through subscription/Advertisement by medical reps.
- Using ARD/NARD meetings for distribution base to increase marketing
- Aiming towards Pubmed indexing
- Updating and Upgrading of our website

OUR REQUEST
As a body, we hereby solicit from the UCH management:
- good connection with UCH internet facilities
- financial support towards the publication of our overdue editions
- meeting and surpassing these projection in record time.

The commissioning we are doing today is an eloquent testimony to the goodwill we as a body is enjoying from the management. Thank you all sir, for all these support, may the Lord continue to bless you.
MULTIPLE PITUITARY HORMONE DEFICIENCY CAUSED BY PIT-1 MUTATION AND THE CHALLENGES OF MANAGEMENT IN A DEVELOPING COUNTRY

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ABSTRACT

Background: In most developing countries, childhood endocrine disorders are not as common as infections but they do occur. Multiple pituitary hormone deficiency (MPHD) is a known cause of familial short stature. This is very rarely diagnosed in Nigerian children.

We describe the challenges of diagnosis and management of childhood endocrine conditions in a developing economy using a ten year old Nigerian girl with MPHD as an illustration.

Methods: Patient had auxological data suggestive of short stature. In order to make a definitive diagnosis, pituitary function tests were carried out in the United Kingdom.

Results: Biochemical tests revealed growth hormone (GH) deficiency, Thyroid Stimulating Hormone (TSH) deficiency, decreased prolactin (PRL) level, normal cortisol and gonadotrophins. Her DNA analysis identified PIT-1 mutation in exon-6. She was placed on recombinant GH and thyroxine with evidence of catch up in height.

Conclusions: There were challenges to management such as, inadequate facility for diagnosis, huge cost of treatment and little awareness about childhood endocrine conditions amongst health workers in a developing economy.

Keywords: Multiple pituitary hormone deficiency (MPHD), PIT-1 mutation, short stature, management, developing country.

INTRODUCTION

Endocrine disorders do occur among children in developing countries, despite the high prevalence of infectious diseases and malnutrition. Reports of endocrine disorders in children in developing countries are few compared to developed countries reflecting the different level of prevalence in the different geographical locations and or level of awareness and availability of facilities for proper diagnosis.

Multiple Pituitary Hormone Deficiency (MPHD) is an endocrine disorder that causes short stature. It may occur as a result of acquired lesions in the hypothalamo-pituitary area such as tumour, surgery, trauma, or irradiation. They may also be idiopathic or result from genetically defined conditions. Congenital MPHD may be familial in 10% of cases, but they are usually sporadic.

MPHD is characterized by impaired production of GH and one or more of the other pituitary hormones. Some developmental genes that play critical role in cell proliferation, cell differentiation and organ commitment such as Hesx1, Lhx3, Lhx4, Prop1, PIT-1, SOX3 and Sox2 have been implicated in MPHD.

These genetic mutations and their inheritance were first shown in mice and then in humans. They present with variable phenotypes.

The PIT-1 gene, the first pituitary-specific transcription factor to be identified in the mouse and human, encodes the POU-domain transcription factor PIT-1 which plays a major role in the normal development of the anterior pituitary gland. It is a 291-amino-acid protein that is essential for the expression of the PRL, GH and TSH genes. PIT-1 is also required for both specification and proliferation of somatotrophs, lactotrophs and thyrotrophs to a limited extent. Therefore, PIT-1 mutations are associated with GH, PRL and TSH deficiencies with TSH being highly variable.
There is very limited data on this condition in Nigerian children. We use this case to illustrate the challenges of diagnosis, management and follow up of this treatable endocrine condition in a developing country and the implications for children with childhood endocrine conditions in general.

**Patient**

Informed consent was obtained from the child and her parents. This 10 year old girl was first referred at the age of 2 years on account of poor growth from birth. She was born at term by spontaneous vaginal delivery, after an uneventful pregnancy. Her birth weight was 2.8kg but her birth length was not recorded. Neonatal period was normal. Parents became worried about her growth from the time she was 2 months of age. She was said to be feeding well. Stool and bowel motions were normal. No episodes of recurrent diarrhoea and/or vomiting. She had no history of chronic cough or breathlessness and she had completed all childhood immunizations. Her developmental milestones were within normal limits.

<table>
<thead>
<tr>
<th>Decimal Age</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI</th>
<th>HeightSDS</th>
<th>WeightSDS</th>
<th>BMISDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.89</td>
<td>72</td>
<td>8</td>
<td>154</td>
<td>-6.08</td>
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<td>5.23</td>
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<td>11.6</td>
<td>17.3</td>
<td>-6.10</td>
<td>-4.16</td>
<td>1.10</td>
</tr>
<tr>
<td>7.34</td>
<td>95</td>
<td>18</td>
<td>19.9</td>
<td>-5.39</td>
<td>-2.06</td>
<td>1.80</td>
</tr>
</tbody>
</table>

**Table 1: Growth Pattern over 4 years**

the age of 2 years on account of poor growth from birth. She was born at term by spontaneous vaginal delivery, after an uneventful pregnancy. Her birth weight was 2.8kg but her birth length was not recorded. Neonatal period was normal. She is the third of three children. Older siblings are of normal height and weight. There is a positive history of short stature in her paternal grandfather. Father's height is 178cm and mother's height is 153cm. She has a mid parental height around the 25th centile.

**Figure 1: Subject's Growth Chart showing height velocity from 2 – 7 years of age**

At presentation, she was small for age. She weighed 8kg with a height of 72cm, which was <0.4th centile for age. Investigations such as chest radiograph, electrocardiography, full blood count, urine culture and urinalysis were all normal. Her haemoglobin electrophoresis is A. Random blood sugar was 49mg/dl, within normal limits. Electrolytes and urea were normal.

At 5 years, her weight was 11.6kg (-4.2 standard deviation score [SDS]) her height was 82.5cm (-6.1 SDS). She had subtle features of GH deficiency. She had a prominent forehead with flat nasal bridge and a rather high palate. She has almond shaped eyes. Her hands and feet were rather cool. Her cardiovascular system was otherwise normal. Her nails were normal but she had short fourth and fifth metacarpals. She had a very prominent fatty abdomen with fatty breasts and a marked lumbar lordosis. Other systems were normal.

She remained markedly short, 95 cm (-5.4 SDS) and had become overweight at 7 years with body mass index (BMI) SDS of 1.8. Table 1 shows her growth pattern over four years. Parents reported that she had developed some psychosocial problems. She had become very conscious of her extreme short stature, she was shy and sometimes manipulative. Figure 1 shows her growth chart with growth velocity from the age of 2.9 years to 7.3 years.

A diagnosis of marked short stature was made but the cause was not defined. The following differential diagnoses were considered, skeletal dysplasia, storage disorder (mucopolysaccharidosis) and GH deficiency. Further investigations were required for which facilities were not available in Nigeria. He was subsequently referred to and reviewed at the Royal Manchester Children Hospital, Manchester, United Kingdom in order to make a definitive diagnosis of the cause of her short stature.

RESULTS

Table 2 is a summary of the anterior pituitary function tests carried out at Royal Manchester Children Hospital, Manchester, United Kingdom. The results revealed

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine Stimulation test - peak GH level</td>
<td>&lt;0.05 mcg/l</td>
<td>low</td>
</tr>
<tr>
<td>IGF-1</td>
<td>33 ng/ml</td>
<td>low</td>
</tr>
<tr>
<td>Prolactin</td>
<td>&lt;50 mu/l</td>
<td>low</td>
</tr>
<tr>
<td>Synacthen Test – Cortisol (nmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>30 minute</td>
<td>667</td>
<td>Normal result</td>
</tr>
<tr>
<td>60 minute</td>
<td>881</td>
<td></td>
</tr>
<tr>
<td>GnRH Test</td>
<td>LH (U/l)</td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>&lt;0.1</td>
<td>1.1</td>
</tr>
<tr>
<td>30 minute</td>
<td>1.7</td>
<td>10</td>
</tr>
<tr>
<td>60 minute</td>
<td>2.6</td>
<td>14</td>
</tr>
<tr>
<td>TRH test</td>
<td>TSH (U/l)</td>
<td></td>
</tr>
<tr>
<td>Basal TSH</td>
<td>3.4 mu/l</td>
<td>normal</td>
</tr>
<tr>
<td>15 minute TSH</td>
<td>3.6 mu/l</td>
<td>normal</td>
</tr>
<tr>
<td>60 minute TSH</td>
<td>3.3 mu/l</td>
<td></td>
</tr>
<tr>
<td>Free T4</td>
<td>9 pmol/l</td>
<td>low</td>
</tr>
</tbody>
</table>

Table 2: Summary of Pituitary Investigations in the United Kingdom
peak GH < 0.05 mcg/l with arginine stimulation test, IGF-I was 33 ng/ml (low) and prolactin was < 50 mU/l (low). TRH test revealed low free T4 of 9 pmol/l, normal basal TSH of 3.4 mU/l and 3.3 mU/l at 60 minutes. There was normal cortisol and gonadotrophins.

These results indicated severe GH deficiency, low thyroxine and a normal basal TSH and a pituitary response to Thyrotropin-releasing hormone (TRH), undetectable prolactin, but normal cortisol response to synaechen and gonadotrophins responses to Gonadotropin-releasing hormone (GnRH). These results are consistent with PIT-1 deficiency. A DNA sample was sent to screen for PIT-1 gene mutations by DNA sequencing.

Figure 2: Result of DNA Analysis for PIT-I Mutation

- Heterozygous c>t change indicated by arrow
- (cgg>tgg, R>W)
- Dominant mutation in PIT-1

Figure 2 shows the result of the DNA analysis for PIT-I Mutation. There was heterozygous c>t change (cgg>tgg, R>W). The dominant mutation was in PIT-1 showing R271W mutation in exon 6.

The patient was subsequently commenced on thyroxine 75 mcg daily and GH at 0.031 mg/kg daily. Table 3 shows her growth pattern over 13 months of GH therapy. Her height had increased by about 12 cm. At the age of 10 years, her height was 117 cm, which is (-3.2 SDS). Figure 3 illustrates the catch up in height evidenced by crossing of centiles on the growth chart. In addition to catch up in height, parents also reported that there was improvement in the psychosocial problems associated with short stature in this child.

**DISCUSSION**

In Nigeria, despite the high burden of childhood infections, endocrine diseases are not uncommon. The Coventry Consensus in 1998 recommended a single height measurement of all children at school entry or around the age of 5 years and prompt referral of children with height less than 0.4th centile for further assessment, in order to identify undetected and treatable asymptomatic growth disorders. This is not carried out routinely as recommended in Nigeria as in many other African countries. Therefore, many cases of short stature are undiagnosed and there is very little data on short stature in Nigerian children. In 1992, Famuyiwa reported 24 cases of short stature in Ibadan, Nigeria. This was a descriptive study as no hormonal data was available in most of the patients and in 4 of them, the cause of the short stature could not be determined. Five of the children were also reported to have idiopathic hypopituitarism. It was not possible to define the cause of the hypopituitarism as we have done in the case reported because of lack of facility. Unlike this reported case, most of them presented first in adolescence. Short stature is not a rare condition in childhood. Early diagnosis is very essential for prompt institution of therapy to enable short children to catch up and achieve normal height.
There are no known reported cases of combined pituitary hormone deficiency in Nigerian children. This is not because these cases are non-existent but due to low level of awareness among health care providers and lack of facilities for diagnosis. This child with PIT-1 mutation is evidence that this condition occurs in African children.

PIT-1 mutations were first described in 1992 by four independent groups\textsuperscript{7-10}. Several mutations have been described subsequently, with a total of twenty-one mutations described to date, and the most frequent being the dominant R271W mutation\textsuperscript{10-12}.

There was lack of facility in Nigeria for definitive diagnosis in this patient. In addition, her parents have to pay for growth hormone therapy. This is a very huge burden for them. The use of GH was evidently of immense value in this patient, not only to make her grow taller, but it contributed to the improvement in the psychosocial problems associated with short stature in this child, enhancing adaptation to a better social life in adulthood.

<table>
<thead>
<tr>
<th>Decimal Age</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI</th>
<th>HeightSDS</th>
<th>WeightSDS</th>
<th>BMISDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.82</td>
<td>105.5</td>
<td>20</td>
<td>18.1</td>
<td>-4.57</td>
<td>-2.35</td>
<td>0.80</td>
</tr>
<tr>
<td>9.43</td>
<td>107</td>
<td>30.5</td>
<td>26.6</td>
<td>-4.66</td>
<td>0.04</td>
<td>2.83</td>
</tr>
<tr>
<td>9.73</td>
<td>117</td>
<td>34.5</td>
<td>25.2</td>
<td>-3.21</td>
<td>0.52</td>
<td>2.52</td>
</tr>
</tbody>
</table>

Table 3: Growth Parameters after starting rhGH

Furthermore, there were other logistic problems with management and follow-up of this patient. GH was
not available in Nigeria and we had to procure it from the United Kingdom. There were also problems with storage of GH, which should be kept refrigerated. There is incessant electricity power cut in the country which can jeopardize the quality and efficacy of GH. There is the need for the policy makers and the government not only to be committed to provision of appropriate equipment and facilities for the diagnosis and management of childhood endocrine disorders in the country but also the management of non-communicable disorders in general. GH and other hormones should be made available in the country so that the cost of shipment can be eliminated.

Furthermore, health care providers in developing countries should have a high index of suspicion when patients present with short stature.

In conclusion, GH therapy has been beneficial for catch up in height in this child. It also improved the psychosocial problems associated with short stature thereby enhancing adaptation to a better social life in adulthood. For the Nigerian child; there are challenges to achieving these goals. The health care providers and the policy makers in Nigeria and other developing countries have an important, significant and urgent role to play in order to improve the outlook and quality of life for African children with endocrine disorders.

REFERENCES


INTRODUCTION

The tympanic membrane lies obliquely across the end of the external ear canal, separating the external and the middle ear.\(^1\) It has three layers derived from the partition between the first branchial groove and the pharyngeal pouch. These are an outer epithelial layer, a middle fibrous layer and an inner mucosal layer.\(^1\)

Tympanic membrane perforation results from trauma to the ear, infective agents, tumours and iatrogenic causes.\(^2,3\) Identified causes include foreign body or unskilled instrumentation or syringing; sudden air compression as in boxing, hand-slap, blast.\(^2,3\) Infective causes could result from acute suppurative otitis media (ASOM) and chronic suppurative otitis media (CSOM).\(^4,4\) CSOM was found to be more common in Nigeria and strongly associated with low socioeconomic status usually resulting in late presentation.\(^5,6,7,8\)

The chronic discharging ear may be serous, serosanguineous, or mucopurulent with wide range of bacteria being cultured.\(^9,10,11\) Usually, size and location of tympanic membrane perforation affects the degree of hearing loss.\(^12,13\) Chronic infection as a result of the perforation can cause major hearing loss.\(^13,14\)

This study aim to determine the pattern and causes of tympanic membrane perforation among patients who presented with ear symptoms and make necessary recommendations.

MATERIAL AND METHOD

This is a one month retrospective study (1/5/2000-31/5/2000) done at the Ear Nose Throat (ENT) Clinic of the University College Hospital (UCH), Ibadan. UCH is the pioneer teaching hospital in Nigeria. All patients that attended the clinic during the period of study with ear symptoms were included in the study. Only patients who did not consent were excluded. Consecutive patients seen during the period of study had their demographic data obtained from them or their patients/guardians who brought them to the clinic after taking their informed consent. Subsequently otological examination for tympanic membrane perforation was performed by ENT surgeons using the head mirror, electric light source and a battery powered otoscope. This data was entered into computer, cleaned and statistical analysis was performed by using SPSS version 11. Ethical consideration included taking informed consent from respondents, using serial numbers and...
not names to maintain confidentiality and making recommendations to appropriate authorities.

RESULTS
A total of 33 patients with tympanic membrane perforation in either or both ears were described in this study out of the 244 patients seen at the ENT Clinic during the month of study. Fifteen (45.5%) were new patients while 18 (54.5%) were follow ups. About half 15 (45.5%) of the respondents were children. There were 13 (39.4%) males and 20 (60.6%) females.

Table 2 showed the type of tympanic membrane perforation. The type of perforation seen were central 57.6%, subtotal 33.3%, total 6.1%, marginal 3.0%.

Table 3 showed the side of ear of respondents affected by tympanic membrane perforation. The sides affected were left ear 45.5%, right ear 15.2%, and both ears 39.4%.

Table 4 showed the cause of tympanic membrane perforation among respondents. The identified causes of perforation were CSOM 90.9%, ASOM 6.1%, and trauma 3.0%.

In children, CSOM was the cause of tympanic membrane perforation. The sides affected in children were left ear 27.3%, right ear 45.4%, and both ears 27.3%.

Figure 1 showed identified types of tympanic membrane perforation in children. Central constituted 64.0% while subtotal made up 36.0%.

DISCUSSION
Tympanic membrane perforation represented 13.5% of the patient seen showing that tympanic membrane perforation is quite common among patients seen at ENT Clinic, UCH. Also about half of these patients with tympanic membrane perforations were children. This is due to the high prevalence of causes of tympanic membrane perforation in these patients especially among the children. CSOM was found to be the commonest cause of tympanic membrane perforation in all age groups which is in keeping with previous studies. In this study CSOM was the cause found in 91% of adults with tympanic membrane perforation and the only cause found in children with tympanic membrane perforation. For example, Okafor BC, 1983 in a study on the pattern of diseases of the ear in SE Nigeria reported that CSOM constituted
44.8% of the defined otological work-load of the out-patient practice. Another study on prevalence of otitis media in school going children in Eastern Nepal reported that although various middle ear pathologies were detected among the children studied, chronic suppurative otitis media was the most common. A study on patterns of ear disease in the Southwestern American Indian reported that CSOM constituted 45% of diseases of the ear seen at their ENT center.

ASOM constituted only 6% of the patients with tympanic membrane perforation in this study. This is most likely because of late presentation of these patients as they might have tried some other forms of care before coming to the clinic. The ENT Clinic is a tertiary referral center receiving patients from the General outpatient and other secondary/primary health care centers all over the state and beyond. Various studies had showed that ASOM precedes CSOM and in populations where the patients reported early, ASOM is more common.

Trauma to the ear accounted for only 3% of the study participants. Studies had showed that traumatic rupture of tympanic membrane are caused by foreign bodies which result in conductive deafness worsened by unskilled attempts at foreign body removal.

In conclusion this study had described the pattern of tympanic membrane perforations and the aetiology among patients attending ENT Clinic, UCH, Ibadan. There is need for detection and quick referral of patients with ear complaints by parents/guardians to ENT surgeons hence need for proper education of parents and guardians on management of ear complaints. Also need to train all healthcare workers especially primary health care providers on management of diseases of the ear.

REFERENCES
PAIN MANAGEMENT WITH NSAIDS: A STUDY OF PATTERN OF USE AND CONTEMPORARY ISSUES

Dr. F. A. Fehintola & Dr. A. A. Ganiyu

ABSTRACT

Introduction: Pain is a cardinal feature of inflammation and is responsible for majority of hospital visits. The non-opioid analgesics possess antipyretic and anti-inflammatory activity and thus are often employed for such purpose of controlling inflammation as well as antipyretic. The non-opioid analgesics are freely available devoid of causing dependence but their potential harmful effects can sometimes be serious. The need for rational drug use is paramount and requires evaluation of physicians practice to serve as basis for continue medical education.

Methods: A retrospective assessment of pattern of prescription at a secondary health facility owned by one of the 36 states of the federation of Nigeria. The age, sex, the drugs prescribed per patient were recorded and prescriptions involving analgesics were further analyzed. Proportions were compared using $X^2$ and statistical significance was set at $p<0.05$.

Results: Analgesic drugs were commonly prescribed constituting 23.8% of all the prescriptions recorded in the study. Paracetamol was the most commonly prescribed analgesic drug accounting for 55.7% of all analgesic drugs prescribed while Dipyron was the most commonly prescribed parenteral analgesic drug. Dipyron accounted for 19% of total Analgesic drug prescriptions but 93% of analgesics administered by intramuscular route. Dipyron was also the preferred Analgesic drug in traumatic conditions. No cognizance was taken of the potential of NSAIDs for causing gastrointestinal injury as Diclofenac, Nimesulide and Dipyron were sometimes used even in patients with peptic ulcer disease.

Conclusions: Pain management with NSAIDs requires some dexterity in particular when certain categories of patients are to be treated. There is need for continue medical education to ensure rational use of these drugs.
to breach renal and gastrointestinal protective mechanisms. However, chronic use of these COX-2 selective agents has been implicated in some cases of sudden cardiac death. The well known classes of nonopioid analgesics include the Salicylates like Acetylsalicylic acid and the Pyrazolones such as Phenylbutazone. Other classes include: Acetic acid derivatives like Indomethacin and Tolmentin, the Oxicams like Piroxicam, Fenamates like Mefenamic acid, Propionic acid derivatives, for example, Ibuprofen, Para-aminophenol such as Paracetamol, and the Alkanone derivatives like Nabumetone.

Other members of the Pyrazolone class of non-steroidal anti-inflammatory drugs include Aminopyrine, Antipyrine, Phenylbutazone, Dipyrone and Oxyphenbutazone. Dipyrone, also known as metamizole, noramidopyrine, novamin sulphone and methampyrone has been available for clinical use since the 1920s. The drug has only weak anti-inflammatory action but analgesic and antipyretic effects are comparable to that of Aspirin. It used to be one of the few non-opioid analgesic drugs available for parenteral use in Nigeria until its ban in the late 2005. The aim of this study was to evaluate the use of Dipyrone and other analgesic drugs in a secondary health facility, indications for their use and possibly consider how well they have been tolerated. We concluded that Dipyrone was commonly prescribed as analgesic and antipyretic at a secondary health facility in Ibadan, South-west Nigeria. There was no documentation of any untoward effects in the over 800 recipients of the drug during the one year period of the study.

MATERIALS AND METHODS
Location of Study
The study was conducted at Jericho General Hospital, Ibadan; a government owned secondary health care facility. The hospital caters for medical needs of patients, mainly adults. Only few children were seen as a hospital established for taking care of children is situated about 1.5 km from this hospital.

Data analysis was carried out using EPI-INFO version 6. Proportions were compared using $X^2$- tests while students t-test was used for continuous variables. Level of statistical significance was set at $p<0.05$.

RESULTS
The total number of prescriptions assessed in the 12 months’ period was 4,323. Of these 1,621 and 2,702 prescriptions were for male and female patients, respectively (table 1). The total number of drugs prescribed was 17,970 drugs. The mean number of drugs per prescription for males was $4.14\pm1.59$ (range 1-7) and for females $4.17\pm1.58$ (range 1-7) drugs.

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Female</th>
<th>Male</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of prescription</td>
<td>2702</td>
<td>1621</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>$31.84\pm14.38$</td>
<td>$32.46\pm17.11$</td>
<td>F: 0.15; $P&gt;0.05$</td>
</tr>
<tr>
<td>Total number of drugs</td>
<td>11252</td>
<td>6718</td>
<td></td>
</tr>
<tr>
<td>Mean drug per prescription</td>
<td>$4.17\pm1.58$</td>
<td>$4.14\pm1.59$</td>
<td>F: 1.63; $P&gt;0.05$</td>
</tr>
</tbody>
</table>

Table 1: Gender distribution of prescriptions for analgesic drugs at Jericho General Hospital, Ibadan, Nigeria
The mean age of female patients was 31.84±14.38 (6-80) and males 32.46±17.11 (3-85) years. Children aged less than 15 years had only 364 or 8.4% of all the prescriptions and 1676 or 9.3% of all drugs. There were similarities between the children population and adult in respect of distribution of various drugs such that in children and adults antimicrobial as well as analgesic drugs were commonly prescribed.

In all, the proportion of analgesics was found to be 23.8% (or 4275). The proportions for antibacterial, antimalarial and other drugs were 15.6% (or 2807), 13.7% (or 2467) and 46.9% (or 8420), respectively. Prescriptions for antibacterial agents were proportionately more for males than females: 1641/6718 (24.4%) versus 1189/11252 (17.7%) respectively; \( \chi^2: 2.48 \) \( P>0.11 \) (table 2).

The proportions of analgesic/antipyretic drugs prescribed for male and female were respectively, 24.4% (or 1641) and 23.4% (or 2634) (table 3). There was no statistically significant difference between the proportions of analgesic drugs prescribed for male and female patients. Of all the prescriptions for analgesics, 812/4275 (19.0%) were Dipyrone 78.6% of all the 1387 prescriptions for injections were for analgesic drugs. The remainder included prescriptions for antihistamines, antibacterial agents, mineral/vitamin supplements, antimalarial and antispasmodic agents. Of the prescriptions for intramuscular analgesic drugs, 638 (or 91.3%) were Dipyrone. Diclofenac and Piroxicam injections were prescribed in 27 (3.9%) and 2 (0.3%) cases, respectively. There were only 32 prescriptions for opioid drugs namely, Tramadol (31) and Pentazocine (1).

The most commonly prescribed analgesic drug, Paracetamol, was prescribed with Dipyrone in 4235 cases and in 30 cases, with other NSAIDs such as Pentazocine (1), Tramadol (3), Diclofenac (3), aspirin (1) and Nimesulide (22). Paracetamol was preferred as mono-analgesic drug in 1928 (81.0%) while Dipyrone was similarly considered in 159 (19.6%) of cases. Treatment of pain of traumatic origin accounted for only 50 of 2381 (2.1%) prescriptions for Paracetamol whereas there were 98/812 (12.1%) prescriptions for Dipyrone for similar condition. In

<table>
<thead>
<tr>
<th>DRUG GROUP</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>1641 (24.4)</td>
<td>2634 (23.4)</td>
<td>4275 (23.7)</td>
<td>( \chi^2: 2.48 ) P&gt;0.11</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>1189 (17.7)</td>
<td>1618 (14.4)</td>
<td>2807 (15.6)</td>
<td>( \chi^2: 35.45 ) P&lt;0.00</td>
</tr>
<tr>
<td>Antimalarial drugs (e.g chloroquine, artesunate, sulphadoxine plus pyrimethamine, etc.)</td>
<td>900 (13.4)</td>
<td>1564 (13.9)</td>
<td>2464 (13.7)</td>
<td>( \chi^2: 0.05 ) P&gt;0.35</td>
</tr>
<tr>
<td>Others including: psychoactive, cardioactive, antiulcer antiviral anti-asthma and Hyperglycemic drugs.</td>
<td>2988 (44.5)</td>
<td>5436 (48.3)</td>
<td>8424 (46.9)</td>
<td>( \chi^2: 48.32 ) P&lt;0.00</td>
</tr>
<tr>
<td>Total</td>
<td>6718 (37.4)</td>
<td>11252 (62.6)</td>
<td>17970</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Frequency distribution of various drugs prescribed compared between males and females (proportions are indicated in parenthesis)
all, there were 155 cases of trauma occasioned by fall, assault or road traffic accident. Thus Dipyrrone was preferred in about 63% of such instances compared to about 32% preference for Paracetamol.

Paracetamol was justifiably preferred for the treatment of pain in patients with peptic ulcer disease and accounted for 86/108 (79.6%) prescriptions for pain amongst such patients. However, Dipyrrone was prescribed in 11 (10.2%), Nimesulide in 9 (8.3%) and Diclofenac in 2 (1.8%) of such instances too. Ibuprofen, Aspirin and other NSAIDs were not prescribed for this population of patients. Except when diagnosis of Peptic Ulcer Disease was made, there was no evidence that efforts were made to include gastro-protective agents in the medication of patients who required NSAIDs. There was also no indication that COX-2 selective NSAIDs were prescribed during the period in review.

Adverse drug reactions were reported in only four cases with Chloroquine accounting for two cases, Pyrimethamine-Sulphadoxine was suspected in one case while overdose of Erythromycin was responsible for the other case. They were all mild reactions requiring only oral medication and outpatient management.

**DISCUSSION**

In this study, male and female patients were similarly represented and both received similar profile of drugs except antibacterial agents which were prescribed more often for males than females. In a tropical environment like ours, most hospitals attendees commonly present with infectious diseases. Other conditions like osteoarthritis, lacerations or cuts, blunt trauma and dislocation/fracture in addition to infectious diseases do require analgesic agents. It is therefore understandable why majority of the prescriptions encountered were for antimicrobial and analgesic/antipyretic agents.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Prescriptions for Analgesics</th>
<th>Oral</th>
<th>Intramuscular injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>2381 (55.7)</td>
<td>2381 (66.6)</td>
<td>-</td>
</tr>
<tr>
<td>Dipyrrone</td>
<td>812 (19.0)</td>
<td>174 (4.9)</td>
<td>638 (91.3)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>61 (1.4)</td>
<td>61 (1.7)</td>
<td>-</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>77 (1.8)</td>
<td>77 (2.5)</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>944 (22.1)</td>
<td>883 (24.7)</td>
<td>61 (8.7)</td>
</tr>
<tr>
<td>Total</td>
<td>4275 (100)</td>
<td>3576 (100.4)</td>
<td>699 (100)</td>
</tr>
</tbody>
</table>

**Table 3: Pattern of prescriptions of Analgesic drugs and routes of administration (percentages are indicated in the parenthesis)**

Paracetamol was justifiably preferred for the treatment of pain in patients with peptic ulcer disease and accounted for 86/108 (79.6%) prescriptions for pain amongst such patients. However, Dipyrrone was prescribed in 11 (10.2%), Nimesulide in 9 (8.3%) and Diclofenac in 2 (1.8%) of such instances too. Ibuprofen, Aspirin and other NSAIDs were not prescribed for this population of patients. Except when diagnosis of Peptic Ulcer Disease was made, there was no evidence that efforts were made to include gastro-protective agents in the medication of patients who required NSAIDs. There was also no indication that COX-2 selective NSAIDs were prescribed during the period in review.

The observation that significantly more men than women received antibacterial drugs during the period under review could not be easily explained. However, such finding may suggest that more men than women presented with infections and/or serious conditions. The prescriptions as revealed in this study were rather skewed such that a lot more prescriptions were for adults. Only few of the children requiring medical attention presented at this hospital as the children hospital is situated nearby. The hospital was set up specifically to cater for the needs of civil servants, thus the preponderance of adult patients. There were similarities between the children population and adult in respect of distribution of various drugs such that in children and adults antimicrobial as well as analgesic/antipyretic drugs were commonly prescribed. Most of the antimicrobial prescriptions were for treatment of either bacterial infections or malaria.

Paracetamol, given at the standard dose is safe and is employed in the treatment of mild to moderate pain of varied origin. The relative absence of major side effects common to other analgesic agents further enhances its acceptability. The drug lacks appreciable effects on both COX-1 and COX-2 and exact mechanism of action remains to be fully elucidated. The choice of Paracetamol in over 50% of the prescriptions for analgesic drugs would be understandable from its tolerability and, in addition most patients presented with acute febrile or painful conditions. The second most commonly prescribed

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analgesic drug was Dipyrone with Ibuprofen placed third. It is interesting to note that Dipyrone was prescribed mainly in the injection form. In fact Dipyrone was the most commonly prescribed parenteral analgesic, accounting for 91.3% of all injections of analgesic drugs encountered in this study. Dipyrone, a Pyrazolone derivative has been banned in a number of European countries and the United States of America following its association with agranulocytosis. In Nigeria, Dipyrone was a very popular analgesic agent until the late 2005 when the drug regulatory agency in the country placed a ban on the use and sale of the drug under a controversial circumstance. Hitherto, indications for its use included post surgical, traumatic pain control and antipyretic effect.

It is of especial note that Dipyrone prescription was proportionately more than Paracetamol for the treatment of pain of traumatic origin. The dearth of effective alternative parenteral analgesic drugs might have been responsible. Agranulocytosis, toxic epidermal necrolysis and other serious untoward effects of Dipyrone were seemingly unknown in Nigeria where the only concern was the pain at injection site. Under-reporting might have been responsible for this observation though, indeed adverse drug events were reported in only four instances in this study. Lack of awareness on the part of the patients and negative attitudes of the physicians could be contributory. However, some recently conducted studies concluded that Dipyrone was safe and efficacious in management of pain of surgical and non surgical origins. Perhaps pharmacogenetics may provide an insight. Meanwhile, it will be essential to carry out a large epidemiological survey with a view to determining tolerance or otherwise of Dipyrone amongst Nigerian Africans.

It is noteworthy that none of the patients with Peptic Ulcer Disease who required analgesic drug was given Aspirin. However, some other NSAIDs were prescribed for some of them. Ideally, this class of drugs should have been avoided in this population of patients.

In conclusion, Dipyrone and other analgesic drugs were commonly prescribed in government owned secondary health care facility in Ibadan, Nigeria. Apparent lack of documentation of adverse effects may be due to attitudinal or genetic differences or yet to be identified reasons. Large prospective country wide study is urgently required to address this issue appropriately.

REFERENCES

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INTRODUCTION

Diabetes is a Greek word which means ‘to pass through ‘urine’. It is a syndrome characterized by disturbed metabolism of carbohydrate, protein, and fat. It is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin. It presents with very different medical and psychosocial issues in children.

Epidemiological studies indicate that there is gradual but steady increase in the incidence of both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) in both developed and developing countries. The manifestations, therapy goals, clinical course, susceptibility to complications of diabetes differ among childhood cases. T1DM accounts for the majority of cases of diabetes in children. Diabetic ketoacidosis may be the initial presentation of T1DM in many children particularly in Africa probably due to low level of awareness.

The focus of this review on T1DM is to provide an overview of the major advances in the aetiology, pathogenesis, and clinical management of newly diagnosed children and their subsequent management with the aim of ensuring optimal growth and development as well as preventing acute and chronic complications. The advances in insulin therapy and regimens and the presentation and management of diabetic ketoacidosis are discussed. The prospects for the cure of the disease are also highlighted in this review.

SUMMARY

Diabetes mellitus (DM) is a syndrome characterized by disturbed metabolism of carbohydrate, protein, and fat. It is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin. It presents with very different medical and psychosocial issues in children.

Epidemiological studies indicate that there is gradual but steady increase in the incidence of both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) in both developed and developing countries. The manifestations, therapy goals, clinical course, susceptibility to complications of diabetes differ among childhood cases. T1DM accounts for the majority of cases of diabetes in children. Diabetic ketoacidosis may be the initial presentation of T1DM in many children particularly in Africa probably due to low level of awareness.

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Key words: Childhood diabetes, glucose monitoring, insulin therapy, DKA, advances

INTRODUCTION

Diabetes is a Greek word which means ‘to pass through ‘urine’. It is a syndrome characterized by disturbed metabolism of carbohydrate, protein, and fat as a result of absolute insulin deficiency (Type 1 diabetes mellitus) or relative insulin deficiency and resistance (Type 2 diabetes). It is the most common endocrine/metabolic disorder of childhood and adolescence. Diabetes can occur in all ages in children.

Classification of Diabetes

DM is a heterogeneous entity which was first classified by the American Diabetes Association in 1979 on the basis of aetiolopathogenesis into four groups, mainly Type1, Type 2, Other types and Gestational diabetes. Table 1 is classification modified from ‘Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus’ in 2000 reflecting all major categories in childhood, including the emergence of type 2 diabetes mellitus (T2DM) and other causes of type 1 diabetes mellitus (T1DM).\(^1\)\(^2\)

Type 1 Diabetes Mellitus (T1DM) refers to childhood diabetes usually associated with autoimmunity and absolute insulin deficiency, although insulin deficiency may not be absolute at clinical onset of the disease.\(^3\) T1DM is further subclassified into Type 1A associated with the presence of islet cell autoantibodies, and Type 1B characterized by the absence of the antibodies.\(^2\)\(^3\)

Type 2 Diabetes Mellitus (T2DM) is childhood diabetes associated with obesity and insulin resistance. Maturity-onset diabetes of youth (MODY), an autosomal dominant DM, is a “milder” form of diabetes caused by specific gene defects that impair insulin secretion.\(^4\) The more severe forms of MODY may require insulin subsequently. Neonatal diabetes is uncommon and usually transient. Permanent neonatal DM has been described, which is usually familial and nonautoimmune.\(^5\)

This review, which focuses mainly on T1DM, provides an overview of the major advances in the understanding of the aetiology, pathogenesis and clinical management of DM in children.
I. Type 1 diabetes (beta cell destruction ultimately leading to complete insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
   A. Typical
   B. Atypical

III. Genetic defects of ß cell function
   A. MODY syndromes
      1. MODY 1 Chromosome 20, HNF-4á
      2. MODY 2 Chromosome 7, glucokinase
      3. MODY 3 Chromosome 12, HNF - 1 á
      4. MODY 4 Chromosome 13, IPF – 1
      5. MODY 5 Chromosome 17, HNF - 18, TCF – 2
      6. MODY 6 Chromosome 2q32, Neuro-D1/Beta-2
   B. Mitochondrial DNA mutations (includes one form of Wolfram syndrome; Pearson syndrome; Kearns-Sayre, diabetes mellitus deafness)
      1. Wolfram locus 2- chromosome
      2. Wolfram mitochondrial
   D. Thiamine responsive

IV. Drug or chemical induced
   A. Antirejection – cyclosporine
   B. Glucocorticoids (with impaired insulin secretion, e.g., cystic fibrosis)
   C. L- Asparaginase
   D. ß – Adrenergic blockers
   E. Vacor (rodenticide)
   F. Phenytoin (Dilantin)
   G. Alfa-Interferon
   H. Diazoxide
   I. Nicotinic acid
   J. Others

V. Diseases of exocrine pancreas
   A. Cystic fibrosis-related diabetes
   B. Trauma-pancreatectomy
   C. Pancreatitis-ionizing radiation
   D. Others

VI. Infections
   A. Congenital rubella
   B. Cytomegalovirus
   C. Hemolytic-uremic syndrome

VII. Variants of type 2 diabetes
   A. Genetic defects of insulin action
      1. Rabson-Mendenhall syndrome
      2. Leprechaunism
      3. Lipoaatrophic diabetes syndrome
      4. Type A insulin resistance-acanthosis
   B. Acquired defects of insulin action
      1. Endocrine tumors-rare in childhood
         a. Pheochromocytoma
         b. Cushing
         c. Others
      2. Anti-insulin receptor antibodies
   VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency.
      A. Prader-Willi syndrome, chromosome 15
      B. Down syndrome, chromosome 21
      C. Turner syndrome
      D. Klinefelter syndrome
      E. Others
         1. Bardet-Biedel
         2. Alstrom
         3. Werner

IX. Gestational diabetes

X. Neonatal diabetes
   A. Transient-cyclic adenosine monophosphate maturation, chromosome
   B. Permanent-agenesis of pancreas
      - glucokinase deficiency, homozygous

Table 1: Etiologic Classification of Diabetes Mellitus

Internationally, there is variation in the incidence and prevalence of T1DM by race, age, season and geographic location. The explanation for these variations is still unclear. Many countries report that incidence rates have doubled in the last 20 years. The rates are highest in Scandinavia especially Sardinia and Finland with annual incidence of 34.4 cases/100,000 and 40 cases/100,000 respectively. In the US, incidence is 15 cases per 100,000 annually and 13.5/100,000 in the United Kingdom. Incidence figures are lowest in Asia and Africa. In China, annual incidence is 1/100,000 and 7.8/100,000 in Libya. In Nigeria, there is a relatively high prevalence rate of 0.33/1000 among school children despite potential deaths caused by minimal medical attention. This is probably due to long-term protein malnutrition and endemic childhood infections, which have been implicated in the aetiology of IDDM in similar populations.

The onset of T1DM has a bimodal pattern with peak incidence at the age of 6-8 years and during puberty but onset in the first year of life is unusual. There is no sex predominance.

The onset of T1DM is seasonal with peak in fall and winter months. This has been suggested as evidence for viral aetiology, but it may also be due to seasonal pattern of higher blood glucose in normal persons during winter.

Pathogenesis
The precise aetiology of T1DM is unknown but some contributory factors have been identified.

Role of autoimmune process
T1DM occurs as a result of environmental factors interacting with a genetically susceptible person. The interaction leads to autoimmune disease directed at the insulin-producing β cells of the pancreatic islets of Langerhans and β cell destruction occurs. B-cell and T-cell autoimmune markers are usually present before the onset of disease suggesting that the autoimmune damage is often insidious. B-cell marker, Islet cell antibody (ICA) is found in 90% of newly diagnosed patients and can be present 20 yrs earlier in at risk groups. Insulin antibodies (IA) occur at disease onset in younger patients while glutamic acid decarboxylase (GAD) antibodies occur in 60-90% of new cases. Insulin deficiency occurs with 90% destruction of β cells which eventually leads to absolute insulinopenia.

Genetic Role
T1DM is not inherited. It is a multifactorial disease with a strong genetic component that is thought to interact with specific environmental triggers. The role of genetic factors in the aetiology is supported by the 30 to 50% concordance rate in monozygotic twins. Several genetic determinants of T1DM have been established. The HLA class II DQ locus on chromosome 6 is the most important, encoding highly polymorphic antigen-presenting proteins that account for almost 50% of the genetic risk for T1D. More recently, high-density genome-wide association studies have been performed to search for the remaining T1DM loci. In all, 18 loci have been identified to date as being robustly associated with the pathogenesis of the disease.

Role of environmental factors
There is 50% to 70% discordance rate of T1DM in identical twins, suggesting that environmental factors may trigger the disease in genetically susceptible individuals. Implicated trigger factors are viruses such as enteroviruses, rubella, coxsackie B, cytomegalovirus, mumps which are postulated to directly initiate damage to β cells. Exposure to certain chemical toxins and drugs that specifically destroy pancreatic cells, such as, rodenticide vacor and streptozotocin, lead to disruption of insulin production. Furthermore, breastfeeding seems to provide protection against the risk of developing T1DM, possibly by direct effect and delayed introduction of cow’s milk. It has been proposed that bovine serum albumin, a protein in cow’s milk with properties similar to islet cell antigen, stimulates autoantibody production leading to destruction of islet cells.

Pathophysiology
Progressive destruction of β cells leads to progressive insulin deficiency. In normal metabolic state, there are regular swings between the postprandial high insulin anabolic state and fasted low-insulin catabolic state that affect three major tissues: liver, muscle and fat as shown in table 2 below.
Relapse - There is irreversible loss of insulin β cell.

Comparison of Fed and Glucose Homeostasis

Total diabetes occurs when there is complete insulin deficiency at clinical presentation.

Remission – partial/complete: Within a few weeks of starting insulin therapy, approximately two thirds of children enter a remission (‘honeymoon’) period during which endogenous insulin production increases. Remission can last weeks to months.

Dehydration occurs when fluid losses exceed intake. Furthermore, insulin deficiency leads to lipolysis with production of excess free fatty acids and ketone bodies leading to ketonuria and metabolic acidosis resulting in compensatory deep rapid breathing (kussmual respiration). Coma may occur due to ketosis, acidosis, dehydration and hyperosmolality.

Clinical Presentation

The classical presenting symptoms of T1DM are polyuria, polyphagia, weight loss and lethargy. Onset may be acute, precipitated by an acute illness, or more chronic and insidious over weeks or even months. Hyperglycemia impairs immunity and renders a child more susceptible to recurrent infections, particularly of the urinary tract, skin, and respiratory tract. Candidiasis may occur, especially in groin and flexural areas. Other features are constipation, anorexia and blurred vision but the younger children, less than 5 years of age are usually asymptomatic except for nocturnal enuresis. There is therefore need for high index of suspicion in this age group to prevent late diagnosis and its consequences such as diabetic ketoacidosis (DKA). In the developing countries, most children present for the first time in DKA partly because of lack of recognition of their symptoms by health workers.

Diagnosis of Diabetes Mellitus

There was a recent revision of the criteria for the diagnosis of DM by the American Diabetes Association’s (ADA) with the definition of a new threshold for the diagnosis of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). The criteria for diagnosis of DM include the presence of at least one of the following:  

(i) Symptoms of hyperglycaemia including polyuria, polydipsia, weight loss plus random plasma glucose concentration >200 mg/dl (11mmol/L).

(ii) Fasting (> 8 hours) plasma glucose > 126 mg/dl (7 mmol/L).

(iii) 2 hour postprandial glucose >200 mg/dl during an oral glucose tolerance test (OGTT).

Criteria for diagnosing IGT and IFG are 2 hour plasma glucose between 140-200 mg/dl (8-11 mmol/L) or a fasting glucose between 100-125 mg/dl (6-7mmol/L) respectively.

Early Clinical Course

The natural history of T1DM is in 4 phases of β cell functional capability.

- Insulin deficiency at clinical presentation.
- Remission – partial/complete: Within a few weeks of starting insulin therapy, approximately two thirds of children enter a remission (‘honeymoon’) period during which endogenous insulin production increases. Remission can last weeks to months.
- Relapse - There is irreversible loss of insulin secretory capacity in patients with remission with abrupt increase in insulin requirement. This can occur gradually or abruptly as a result of intercurrent infections.
- Total diabetes occurs when there is complete insulin deficiency as a result of lack of endogenous insulin secretion. Glycaemic control with subcutaneous insulin becomes more difficult and glycemic excursions more profound.

Investigations

At initial diagnosis of T1DM, it is important to carry out investigations such as:

1. Blood glucose: Diagnosis is confirmed when there are classic symptoms and one random blood glucose
They should be encouraged to establish basic skills for long-term management of diabetes when hyperglycaemia or glycosuria occur as a result of intercurrent illness, steroid therapy or when the patient’s condition includes renal glucosuria. Stress hyperglycaemia (a transient increase in blood glucose during acute stress) may be differentiated from new onset diabetes by its short duration (1-5 hours) and without insulin treatment, glucose levels return to normal.

2. Urine glucose: Glycosuria is suggestive of DM and not diagnostic.
3. Urine ketones: Ketonuria is a marker of insulin deficiency and potential DKA. Its presence generally confirms that diabetes is T1DM.
4. Islet cell antibodies, IA and GAD may be present at diagnosis but are not needed to diagnose T1DM.

Management of Type 1 Diabetes Mellitus
Managing children and adolescents with DM is complex and requires multidisciplinary team including a paediatrician with expertise in diabetes, diabetes nurse specialist, dietitian, psychologist, health educator and social worker. The goals of treating a child with DM are to achieve (i) normal growth and development, (ii) prevent acute complications such as severe hypoglycaemia which when recurrent, is associated with risk of developing learning disabilities and neurologic deficits in children less than 5years and (iii) prevent chronic complications by achieving near normal blood glucose. Duration of hyperglycaemia is the most important risk factor for chronic complications of T1DM. The management of DM can be divided into long-term management and management of acute complications primarily diabetic ketoacidosis (DKA).

Long Term Management
At initial diagnosis, hospitalization may not always be required except in children with the following conditions: (i) diabetic ketoacidosis, (ii) age less than 5 years, (iii) parents with difficulty understanding the management program and/or serious psychosocial problems, (iv) children with psychomotor delay, (v) families who live outside the region.

The basic components of long-term management of T1DM are education and emotional support, diet and insulin therapy.

Dietary Management
This is an essential component of diabetes care. A paediatric dietician should provide education, monitoring, and support to the child, parents and extended family. The dietician should advise on planning, content, and timing of snacks/meals in the context of each child’s individual circumstances, lifestyle, and the insulin action profiles. The dietary recommendations should be based on healthy eating recommendations appropriate for all children and adults and the whole family should be encouraged to make appropriate changes.

Basic universal recommendations are that carbohydrates should provide 50-60% of daily energy intake and no more than 10% should be from sucrose or other refined carbohydrates. Fat should provide less than 30% and protein should provide 10-20% of daily intake. The aim is to balance the child’s food intake with insulin dose and activity and to keep blood glucose concentrations as close as possible to reference ranges of 80-180mg/dl.

Insulin Therapy
Insulin is required for treating all forms of diabetes. It was isolated in 1921-22 at the University of Toronto by Banting, Macleod, Best and Collip. There are 3 species of insulin - Porcine, Bovine and Human insulin. Their onset of action, efficacy and side effects are similar, but human insulin is recommended for children with diabetes.
**Advances in Insulin Therapy**

The most recent advance in insulin therapy was the development of insulin analogues with the overall aim that administered insulin would mimic the physiological release of insulin during the post-prandial and post-absorptive periods.²⁴-²⁵

Table 3 shows currently available insulin analogues, their onset and duration of action.

Ultra-short acting insulin analogues are very rapid-acting (RA) and exist as monomers, thus absorbed in minutes. They are injected immediately before food and allow for greater flexibility of meal time. This leads to improvement in glycaemic control with fewer episodes of hypoglycaemia.²⁴-²⁵ Examples of ultra-long-acting insulin analogues are Ultralente, Glargine. They lead to consistent and prolonged insulin release with no peaks and constant basal insulin concentration. This leads to better glycaemic control, less nocturnal hypoglycaemia and good safety data.²⁶

Many non-invasive routes for insulin administration have been investigated including nasal, buccal, oral, gastrointestinal, and transdermal. There has been maximum progress with the inhaled route.²⁷ It is an insulin analogues with the aim of delivering insulin in more convenient manner than the traditional subcutaneous route, thus it may be especially useful for patients with needle phobia.²⁸ It has been shown that when inhaled insulin is taken before meals in addition to a basal insulin injection, it leads to good glycaemic control similar to that of patients given multiple dose injections (MDI).²⁹ However, the long term safety and efficacy of inhaled insulin is yet to be established.²⁴

**Insulin Delivery Devices**

Insulin can be delivered with syringe and needle. Semiautomatic pen injector devices, disposable (prefilled) or reusable are now available and generally preferred by children as they are quicker and easier to use than syringes and needles.²⁸ Insulin can also be administered with insulin pumps. They are programmable pumps containing insulin connected by infusion line to a small plastic cannula inserted subcutaneously.²⁸

<table>
<thead>
<tr>
<th>Duration</th>
<th>Time to Onset</th>
<th>Time to Peak</th>
<th>Duration of action (hrs)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-long-acting (LA)</td>
<td>1-2 hrs</td>
<td>10-14 hrs</td>
<td>23-24</td>
<td>Glargine, Detemir</td>
</tr>
<tr>
<td>Intermediate-acting (IA)</td>
<td>30-60mins</td>
<td>4-8 hrs</td>
<td>8-12</td>
<td>Insulatard</td>
</tr>
<tr>
<td>Short-acting (SA)</td>
<td>30mins</td>
<td>1-2 hrs</td>
<td>6-8</td>
<td>Human Actrapid</td>
</tr>
<tr>
<td>Ultra-short-acting (RA)</td>
<td>10 mins</td>
<td>30-60mins</td>
<td>2-5</td>
<td>Novorapid Lispro</td>
</tr>
</tbody>
</table>

**Table 3: Onset and Duration of Action of Insulin Analogues**

**Insulin Regimens**

The aim of insulin therapy is to mimic the physiological secretion of insulin. At diagnosis, as a rule of thumb most pre-pubertal children will require 0.5 to 1 unit/kg/day of insulin. Adolescents may require up to 2 units/kg/day.²⁸ This requirement may be reduced substantially in the first few months of therapy during the honeymoon period.²⁸ There are various regimens. When choosing a regimen, we should bear in mind the needs and wishes of the family and make changes, if there are difficulties or poor glycaemic control.

1. **Traditional regimen** – this is the use of twice daily injection using a mixture of ultra-short-acting (RA) or short-acting (SA) and intermediate-acting (IA) insulin. About one third is given as RA/SA and two-third as IA formulation. About 60-70% of total daily dose is given at bedtime as LA and 60% to 70% is given as RA/SA and split between the three meals.

2. The **Basal/bolus regimen** – Basal bolus regimen can be given by multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) which uses only rapidly acting insulin. MDI is the use of RA/SA prior to each main meal with an injection of LA prior to bedtime. It suppresses glucose production between meals and overnight. Usually 30% to 40% of total daily dose of insulin is given at bedtime as LA and 60% to 70% is given as RA/SA and split between the three meals. It allows greater variation in meal times and size of meals.³⁶,⁴⁰

3. **Continuous Subcutaneous Insulin Infusion (CSII)** – the use of insulin pump therapy. It is used in about 25% of children in the USA and about 1-2% in the United Kingdom. They may be used as
part of an intensive management regimen to improve glycaemic control. The devices consist of a programmable pump containing insulin connected by an infusion line to a small subcutaneous cannula. One injection site is used for 2-4 days, hence there is less variation in absorption due to site rotation and insulin delivery allows closest match to physiological requirements. The pump delivers RA/SA insulin continuously at a basal rate with additional boluses delivered at meal time. Pump therapy is said to provide the best and most consistent glycaemic control. It should be used only by a trained and experienced team.28,40

Problems of Insulin therapy
- Somogyi phenomenon – This is the rebound morning hyperglycaemia which may occur following nocturnal hypoglycaemia caused by release of counter regulatory hormones (GH, glucagon, cortisol & adrenaline).22
- Dawn phenomenon - This is hyperglycaemia as a result of hypoinsulinaemia which occurs between 5-9am. It occurs mainly in puberty and is thought to be due to insulin resistance caused by nocturnal GH secretion.22

Blood glucose monitoring
The level of long term glycaemic control determines significantly the risk of developing chronic microvascular complications of diabetes, therefore, it is important to maintain blood sugars as near normal as possible and prevent the risk of hypoglycaemia. Therefore, regular home blood glucose monitoring should be carried out for the success of intensive management of diabetes.29 Generally, a blood glucose level of 100-200mg/dl (6-12 mmol/L) for preschool children, 72-180mg/dl (4 -10 mmol/L) for older children and 72-144mg/dl (4 -8 mmol/L) for adolescents should be the aim.24

Routine follow up
Children and their parents should be seen regularly in a designated clinic for follow up by the diabetes team every 3 to 4 months and assessed for the following:28,30
- general health, including height, weight, blood pressure, hospital admissions;
- Review of blood glucose monitoring, insulin regimen and details of hypoglycaemic episodes
- comparison of glycemic control with glycosylated hemoglobin (HbA₁c)
- accuracy of the glucose monitor compared with laboratory blood glucose testing equipment;
- meal plan requirements and adherence;
- knowledge of diabetes, insulin, and diet;
- insulin injections and examination of injection sites
- attitudes to and management of diabetes, psychosocial problems and school progress

Children should also be screened for conditions associated with diabetes and for long-term complications.

Patients who have had diabetes for 2 years or more should have annual review with physical examination for microvascular & other complications of DM including fundoscopy as detailed in table 4.

<table>
<thead>
<tr>
<th>System</th>
<th>Points to note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>Growth failure</td>
</tr>
<tr>
<td>Weight</td>
<td>Poor or excessive weight gain</td>
</tr>
<tr>
<td>Puberty</td>
<td>Delayed puberty/amenarche</td>
</tr>
<tr>
<td>Skin</td>
<td>Lipohypertrophy; necrobiosis lipoidica</td>
</tr>
<tr>
<td>Mouth</td>
<td>Dental caries or signs of poor oral hygiene</td>
</tr>
<tr>
<td>Eyes</td>
<td>Retinopathy/cataracts</td>
</tr>
<tr>
<td>Feet</td>
<td>Signs of poor foot care e.g. calluses</td>
</tr>
<tr>
<td>Hands</td>
<td>Limited joint movement</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Goitre, signs of hypo- or hyperthyroidism</td>
</tr>
<tr>
<td>Neurological</td>
<td>Impaired vibration and pinprick sense; loss of ankle reflex</td>
</tr>
</tbody>
</table>

Source – Reference 28

Table 4: Points to note on examination of patients with DM at annual review

They should also have the following investigations:28,30
1. Glycated hemoglobin (HBA1c) - best method for medium- to long-term diabetic control monitoring. Levels should be checked every 3 months. Most clinicians aim for HbA1c values of 7-9%.
2. Thyroid function tests - Untreated thyroid disease may interfere with diabetes management so thyroid function should be checked annually if thyroid antibodies are present.
3. Screening for coeliac disease by measurement of celiac antibodies annually.
4. Screening for microalbuminuria - From age 12 years, annual urinalysis needed to test for a increased albumin excretion rate (AER), referred to as microalbuminuria, which is an indicator of risk for diabetic nephropathy
5. Lipid profiles - Children should also be screened intermittently for lipid abnormalities (fasting serum lipid profile 6 months after diagnosis and again during adolescence or when diabetic control is poor.
6. Renal function tests: If the child is otherwise healthy, tests typically are not required.
Complications of Type1 Diabetes Mellitus

There are 3 major categories:

- Acute complications - reflect the difficulties of maintaining a balance between insulin therapy, dietary intake, and exercise.
- Long-term complications - Chronic complications of diabetes in childhood and adolescent result from poor glycaemic control. Complications include short stature with delayed maturation, limited joint mobility commonly affecting the interphalangeal joints and adolescent microvasculopathy, neuropathy and microalbuminuria.
- complications caused by associated autoimmune diseases

Acute Complications

These include: DKA, hypoglycemia, and hyperglycemia. The commonest acute complication of T1DM is DKA and will be discussed in detail.

Diabetic Ketoacidosis (DKA)

Diabetic Ketoacidosis creates a life-threatening medical emergency. Therefore, early recognition and careful management are essential if death and disability are to be avoided. DKA may be the initial presentation of T1DM and is the most important cause of mortality and severe morbidity in children with diabetes, particularly at the time of first diagnosis. In Africa, it is the most frequent cause of death in patients with T1DM. It may occur as a result of an intercurrent illness or recur if insulin is omitted (recurrent DKA in adolescence is almost always due to insulin omission). The clinical features of DKA are severe dehydration, shock, frequent vomiting, polyuria despite dehydration, weight loss in spite of good intake, acetone breath – (Kussmaul respiration) deep and rapid, altered sensorium and signs of raised intracranial pressure such as bradycardia, hypertension and anisocoria. Diagnosis can be made on clinical and biochemical grounds. The biochemical criteria for the diagnosis of DKA include hyperglycaemia (glucose >200mg/dl/11mmol/l), metabolic acidosis (bicarbonate < 15mmol/l) and venous PH <7.30 with ketonuria (serum ketones >5mmol/l).

Management of DKA

DKA is a medical emergency and like all emergencies, resuscitation should follow the ‘ABC’ pattern. The protocol described is largely based on that published by the European Society for Paediatric Endocrinology and the Lawson Wilkins Paediatric Endocrine Society and by the British Society for Paediatric Endocrinology and Diabetes.

Resuscitation

- Admit to the intensive care unit or high dependency unit if pH<7.00, age < 2 years, unconscious and blood glucose >1000mg/dL
- Resuscitation in ABC pattern
- If in shock, oxygen by face mask should be given.
- If signs of shock (i.e hypotension, severe peripheral shut-down, oliguria) are present, resuscitate with boluses of 10 ml/kg of 0.9% saline, or 0.9% saline plus 5% albumin. Repeat as necessary, and then place on maintenance + deficit. Replace fluid requirement over 48 hours. If the corrected serum sodium value is in the hypernatraemic range, even slower rehydration may be considered.

Initial Monitoring

- Hourly pulse rate, respiratory rate, blood pressure, neurological observations.
- Hourly blood glucose measurement while on an insulin infusion.
- Accurate fluid balance (an indwelling catheter may be required).
- 2-4 hourly temperature
- Test all urine for ketones until negative.
- Strict fluid balance is essential. Reassess fluid status every few hours. Continuing polyuria may worsen the dehydration if a positive fluid balance is not being achieved. The patient initially should be “Nil by Mouth.
- Insert a sampling cannula and obtain blood samples for:
  - Baseline blood glucose, electrolytes, calcium, phosphorus, venous pH and acid base status (arterial if signs of shock are present), full blood count, urea and creatinine, triglycerides and sepsis work up if indicated.
  - urine test for ketones and microscopy, culture and sensitivity.
  - Do 2-4 hourly electrolytes and venous pH, depending on severity and progress.

Electrolyte Replacement

- Sodium replacement is individualised on the basis of biochemical monitoring. The measured serum sodium concentration is lowered by the dilutional effect of the coexistent hyperglycaemia and coexistent hyperlipidaemia. An approximate corrected sodium can be calculated as follows: Corrected sodium = Sodium + 1.6(glucose – 5.5) 5.5 (all values in mmol/l)
• If corrected sodium is greater than 150 mmol/L, correction of the dehydration and electrolyte imbalance over 48-72 hours is advocated to minimize the risk of cerebral oedema.
• Potassium replacement should be started as soon as resuscitation is completed and prior to commencing the insulin infusion. If renal failure is suspected, withhold potassium until electrolytes are available and an indwelling catheter is inserted.
• Commence potassium chloride at 5 mmol/kg/day. Check serum potassium 2 hours later and then 4 hourly.
• Bicarbonate therapy is generally not required. It may be considered after consultation in the severely shocked patient with severe acidosis (i.e. arterial pH <7.0 and/or HCO₃⁻ <5mmol/L). Cardiac monitoring is required; hypokalaemia and exacerbation of hypernatraemia are risks. Bicarbonate should be given by an intravenous infusion over 30 minutes.

**Insulin Infusion**

- Start after resuscitation is completed and rehydration and potassium replacement is under way.
- Add 50 units of short-acting insulin to 500 ml of 0.9% Saline, so that 10 ml of solution will contain 1 unit of insulin. If an infusion pump is not available, a soluset may be used.
- The insulin infusion must be clearly labeled so that confusion with the rehydrating solution does not occur.
- Start the insulin infusion at 0.05-0.1 units/kg/hr. It is not necessary to give a priming bolus of insulin.
- The aim is to produce a fall in blood glucose of 72-90mg/dl (4-5 mmol/L) per hour. Over the first two hours, however, rehydration alone will result in a fall in blood glucose and a larger fall can be accepted at this time without a reduction in insulin infusion rate.
- If plasma glucose concentrations fall by more than 90mg/dL/hour add dextrose (5-10%) to the intravenous fluids.
- When the blood glucose has fallen to 14-17 mmol/L (250-300mg/dL), intravenous fluid with dextrose should be prescribed (usually a 5% dextrose/0.45% saline mixture is used, but dextrose concentrations of up to 10% may be necessary to maintain plasma glucose concentrations).
- The insulin infusion rate and/or the Dextrose infusion rate should then be adjusted to keep the blood glucose level between 140 – 220 mg/dl (8-12 mmol/L).
• The insulin infusion should not be stopped before the acidosis is corrected as insulin is required to switch off ketone production. If the blood glucose falls <4mmol/L, (<72mg/dL) a bolus of 2ml/kg of 10% dextrose should be given and the dextrose concentration in the fluid increased.
• When the pH is >7.30, the blood glucose concentration has been reduced to 14-17 mmol/L (250-300mg/dL), and a dextrose infusion has been started, the insulin infusion rate can be reduced – but not to less than 0.05 units/kg/hour.
• If the patient still requires IV fluids after 24 hours, use 0.45% saline in 5% Dextrose.

**Subsequent Management**

- Although plasma glucose concentrations may fall to near normal levels within 4-6 hours of treatment of DKA, the metabolic acidosis may take 24 hours or longer to resolve.
- Blood gases and electrolyte and urea concentrations should be re-evaluated 2 hours after the start of treatment and 4-hours thereafter, or more frequently if there are clinical concerns, until the child has recovered.
- The ongoing intravenous fluid prescription should be reviewed every 4 hours and adjusted according to the electrolyte results and fluid balance.
- If there is continuing massive polyuria, the rate of infusion of intravenous fluids may need to be increased and large gastric aspirates will need replacing with 0.45% saline with 10mmol/L potassium chloride.
- Once the blood gases and electrolyte concentrations normalize, the frequency of blood sampling can be decreased and discontinued once the child is tolerating oral fluids and food.
- The frequency of bedside capillary blood glucose measurements may be reduced to 2-to-4-hourly if plasma glucose concentrations are relatively stable while the child is receiving intravenous dextrose.
- If the acidosis or hyperglycaemia do not improve after 4-6 hours the patient should be reassessed by a senior doctor. Insulin errors, inadequate rehydration or sepsis may be the cause. More insulin, 0.9% saline or antibiotics may be required.
- Intravenous fluids should be continued until the child is drinking well and able to tolerate snacks.
- The insulin infusion should be continued until significant ketonuria (++) is no longer present. However, it is not necessary to wait for complete resolution of ketonuria before changing to subcutaneous insulin.
- When the patient is started on a conventional subcutaneous insulin regimen, the insulin infusion should be discontinued 30 minutes (if using a short
and long-acting insulin) after the first subcutaneous injection to avoid rebound hyperglycaemia.

Cerebral Oedema

This can be a sudden and unpredictable complication of the therapy of DKA which occurs in the first 24 hours of treatment. It is commoner in children younger than 10 years (especially < 5 years). The aetiology is poorly understood because it could occur even with optimum management of DKA. It is associated with 25% mortality and neurological sequelae in survivors. All patients should therefore be monitored for signs and symptoms of raised intracranial pressure. Risk factors and warning signs include severe dehydration and shock, severe acidosis and low serum potassium indicating severe total body loss of potassium, hypernatraemia indicating a hyperosmolar state, hyponatraemia, and deteriorating conscious state during therapy. If suspected it requires treatment immediately with mannitol 1-2 g/kg by intravenous infusion over 20 minutes. The rate of fluid administration should be reduced. Transfer to an intensive care facility and arrange a neurological assessment and CT scan.

Prospects for the Cure of Type 1 Diabetes

The mainstay of treatment for T1DM is currently lifelong insulin therapy. However, cure of the disease is being sought through various treatment protocols including those aimed at replacing β cells via pancreatic organ transplantation or islet cell transplantation. These are:

- Efforts at prevention and early diagnosis through genetic and immunologic screening of high-risk children.
- Development of new and improved insulins.
- Administration of insulin by alternate routes like nasal, inhalation.
- Improvement in the management and outcome of pancreatic and islet cell transplantation.

Pancreatic and islet cell transplantation

Pancreatic transplantation was first reported in 1966 with significant improvement in operative techniques and immunosuppressive drugs over the years. Pancreatic transplantation is not generally recommended in children because of the risks of surgery and prolonged immunosuppression. Successful islet cell transplantation was first reported in 1980 and recent advances in immunosuppressive therapy and transplant biology with the development of the regimen called Edmonton protocol led to very good result of 80% rate of insulin independence and euglycaemia at 1 year post-transplant. However, longer term follow up has tempered enthusiasm for this strategy.

Techniques are now underway to develop stem cell therapy to isolate and propagate islet cell progenitor cells from adult pancreas or extrapancreatic sources suitable for transplantation.

In conclusion, T1DM is not uncommon in African children despite the paucity of data on the epidemiology in Africa. It is an autoimmune disorder that is usually triggered by some environmental factors in genetically susceptible individuals. DKA may be the initial presentation of T1DM and is the most important cause of mortality and severe morbidity in children with diabetes, particularly at the time of first diagnosis. In Africa, it is the most frequent cause of death in patients with T1DM. The risk of complications relates to diabetic control. With good management, patients can expect to lead full, normal, and healthy lives. Mortality and morbidity associated with T1DM diabetes has perceptually declined with the identification and widespread use of newer insulins and automated methods of delivery via programmable pumps. Furthermore, there are prospects in islet cell transplantation and the development of stem cell therapy for future cure of the disease.

Sadly, this remarkable achievement has not reached the children who develop diabetes in sub-Saharan Africa where the onset of childhood diabetes may be the equivalent of a death sentence. Two major issues of importance related to T1DM in developing countries are missed diagnosis and unavailability of insulin.

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INTRODUCTION
Diabetes is frequently associated with acute metabolic complications. Acute complications occurring in diabetes can broadly be divided into metabolic and non-metabolic. The non-metabolic complications include severe infections such as sepsis, malignant externa otitis etc. The focus of this section however will be on the acute metabolic (hyperglycaemic) complications which include: Diabetic Ketoacidosis (DKA), Hyperglycaemic Hyperosmolar State (HHS) and lactic acidosis. Lactic acidosis rarely occurs now because phenformin, a type of biguanide and the commonest causative drug agent is no longer in use. However lactic acidosis can still occur in some clinical situations like shock, cardiac, hepatic or renal decompensation, especially in the patients receiving metformin (biguanide) for treatment of diabetes. We shall therefore restrict ourselves to DKA and HHS which together constitute hyperglycaemic emergencies (HE) for the purpose of this article.

DKA by definition consists of the occurrence of a triad: hyperglycaemia, ketonaemia and high anion gap metabolic acidosis. HHS (old terms were “hyperglycaemic hyperosmolar non-ketotic state or coma) is similar but different from DKA in that ketonaemia is minimal, hyperglycaemia and osmolality are much higher and consequently, dehydration is more severe. The underlying pathophysiological problem is absolute (DKA) or relative (HHS) deficiency of insulin with increase in the concentration of counterregulatory hormones especially glucagon. Any unconscious patient who is dehydrated should have his/her blood glucose quickly checked. The clinical presentation of DKA and HHS are similar, though with few areas of major difference. The patient with DKA is usually young and lean while HHS is usually elderly. Both present with prostration, polyuria, polydipsia and often have alteration in level of consciousness. Major areas of differences are that clinical evolutions of symptoms tend to be relatively more rapid in DKA than HHS, usually over a period of 2-3 days. Patients with DKA may also present with nausea and vomiting, and occasionally abdominal pain. Kussmaul (fast and deep) breathing may occur in both types, but especially in DKA. Other physical findings include dehydration, tachycardia and hypotension.

Epidemiology
The incidence of HE is increasing worldwide. The annual incidence of DKA from population-based studies is estimated to range from 4 to 8 episodes per 1,000 patient admissions with diabetes. There is rarity of data on the annual incidence of HE in Nigeria. Even then, HE are leading causes of death in Nigeria. Although the mortality rate of these complications is reducing in Western developed countries, the situation has not changed in developing countries like Nigeria. Okoro and co-workers in Ilorin reported a crude
mortality rate of 22% and 25% for DKA and HHS respectively. In a retrospective study in Ife involving 144 diabetic patients, DKA was the commonest cause of death out of 25 deaths recorded in the 6 years of study. More recently, Ogbera and co-worker reported a crude mortality rate of 20% among 111 diabetic patients in Lagos. A combination of factors are responsible for this high mortality, including a poor and inefficient health system- especially grossly poor laboratory support, shortage of well-trained qualified health personnel, ignorance about diabetes and its acute complications. Perhaps the biggest factor is financial constraints, seen in majority of the patients who, together with their relatives directly bear the cost of healthcare in Nigeria.

It is important that HE be prevented in Nigeria, not only because it is an important cause of premature death in patients with diabetes, but also because the average individual cannot afford the cost of treatment. In the United States of America where direct and indirect costs of management can be readily quantified, it has been reported that the average cost per patient per hospitalization is $13,000. Moreover, at present the country cannot boast of a robust and efficient healthcare system not to talk of modern facilities in most places to effectively manage HE. This latter reason perhaps underpins the vexatious high mortality rate in Nigeria. Therefore the only rational way is prevention. Fortunately, HE can be prevented to a great extent. However strategies for prevention must be crystallized and rigorously instituted in order to stem the burden of mortality resulting from hyperglycaemic emergencies (HE).

Precipitating factors
Identification of precipitating factors is crucial to formulating an effective prevention strategy for HE. The 2 commonest precipitating factors of HE globally, in order, are infections and inadequate or inappropriate insulin therapy. Although this is also true in our environment, emerging data in Nigeria and Africa showed that problems with insulin therapy is fast becoming the number one reason for developing HE. This is not surprising because of the prevalent poverty and limited availability of insulin in some places. The usual reasons for omitting insulin among diabetic patients include financial handicap to procure drug regularly. In fact many patients resort to self-directed reduction of insulin dosage and frequency of dosing in order to delay procuring another vial. Insulin is also omitted due to ill health and erroneous belief that drugs should not be taken when ill, use of alternate herbal remedies and cultural misperception about use of insulin. Quite often, patients present for the first time in HE, without being previously diagnosed as having diabetes. This mode of presentation is not only common in patients with type 1 diabetes presenting with DKA but is also frequently seen in type 2 patients presenting with HHS. Comorbid illnesses such as stroke, myocardial infarction, and pancreatitis may also precipitate the conditions. Drugs such as steroid, thiazide diuretics, propanolol, phenytoin and alcohol are notable precipitants. Sometimes physical or emotional stress may be the trigger, especially among young females. In about 1-2% the precipitating agent may not be identified.

Strategies for Prevention
It has been shown that when carefully thought and locally adaptable strategies are instituted, mortality from HE can significantly be reduced as the case in South Africa. In a South African community, strategies formulated and implemented were found to cause a 15% reduction in mortality of HE 5 years later. One interesting finding in this study is that education of both patients and doctors can significantly reduce mortality.

Education. At the core of preventive measures is patient’s education and empowerment. Prevention of hyperglycaemic emergencies is basically about focusing on the usual precipitating factors and empowering the patient through education to know how to avoid the precipitating factors or institute early intervention to prevent progression to full-blown emergencies. Patients with diabetes must acquire basic knowledge and skills on how to intelligently cooperate with the healthcare team in order to prevent sinister acute and chronic complications of diabetes. There should be a regular creation of awareness among the general public about diabetes and its untoward complications. People, especially those at risk of developing diabetes should be encouraged to go for screening tests. Those who are already diabetic must be taught the value of Self Monitoring of Blood Glucose (SMBG), analysis of glycaemic records and implications of different glucose readings. Furthermore, they must be taught how to handle sick days; for example, not to stop their anti-diabetic drugs, eat foods that are easy to digest and drink sugar-free fluids when appetite is suppressed or lost. They must be counseled to promptly communicate with and/or contact their doctors. This is now made relatively feasible with the advent and widespread use of mobile phones by the average Nigerian, even those in the low socio-economic strata. An emergency line can be created in the hospital by the healthcare team through which patients can readily reach their care-givers. Capacity building through periodic training of the healthcare personnel especially doctors and nurses must be ensured in order to deliver optimum and effective care of patients with diabetes.
and thereby prevent development of acute complications or to abort a smoldering HE from progressing to full blown emergency. In this regard, a locally workable and adaptable protocol for management of HE is required and overdue.

Restructuring healthcare system: Recommendation to institute effective diabetes education for patients and training of healthcare personnel draws attention to the fundamental need to critically appraise and restructure our healthcare system. This is because maximum and lasting benefits can only be reaped from measures advocated above if we have in place a robust and efficient healthcare structure. Okoro and his team in Ilorin, observed that about half of the 40 patients with HE in their cohort had attended the diabetic clinic at some point prior to hospitalization\(^5\). This signifies a failure of the health system in that place and is most probably true of the entire country. There are worthy examples in Africa, such as Ghana\(^1^4\) and South Africa\(^1^5\), where novel healthcare models for care of diabetic persons have been devised and implemented with significant positive impact on diabetes care. The present healthcare structure and system in Nigeria restrict accessibility to health facilities and will not support high quality care of persons living with diabetes. In a previous work, Adeleye et al advocated for measures to achieve a major increase in awareness and knowledge about diabetes, its complications and prevention amongst Nigerian health professionals especially at primary and secondary healthcare levels\(^1^6\). The introduction of Village Health Workers and establishment of diabetes centres were also suggested. All this calls for a radical restructuring of our healthcare delivery system.

Healthcare financing: Issue of compliance with medications at whatever level should receive compassionate counseling by the managing team. This is because in our environment at present, most patients are on the low socio-economic rung and worse still, are paying medical bills from their pockets with no effective insurance aid. The reality is that only a few percentage of the populace can self-finance their healthcare needs, especially a chronic, life-long health condition like diabetes. Government should speed up the process of ensuring effective health insurance scheme for the people. Availability and subsidy of anti-diabetic drugs, especially insulin should be guaranteed by the government. Professional bodies like the endocrine associations as well as the Diabetes association in Nigeria must, backed by data of prevalence, incidence, mortality and morbidity of HE, use every opportunity to draw the attention of government to the appalling situation of our healthcare system and infrastructures, particularly as it concerns diabetes care. It is this kind of intense and persistent advocacy that will cause government to realize that non-communicable diseases are taking an equally severe, if not more toll on the health of Nigerians like the communicable diseases.

Hyperglycaemic emergencies are preventable. Mortality and morbidity can and should be reduced by identification of the risk factors, effective education and empowerment of the diabetic patients, training of healthcare personnel and critical appraisal and restructuring of our health system with the government giving more than a passing attention to the plight of citizens living with diabetes.

REFERENCES


UNCOMPPLICATED MIDVAGINAL VESICO-VAGINAL FISTULA REPAIR IN IBADAN: A COMPARISON OF THE ABDOMINAL AND VAGINAL ROUTES

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ABSTRACT
Background: Obstetric fistula is a resultant effect of prolonged obstructed labour. The best surgical management of simple uncomplicated fistula determines the outcome of care.
Objective: To compare outcome of uncomplicated mid-vaginal fistula between vaginal and abdominal route of repair.
Materials and Method: This was a hospital based retrospective study conducted at the University College Hospital, Ibadan from January, 2000 till December, 2006.
Result: Of the 71 midvaginal fistulae managed, 40.8% had abdominal repair while the remainder were through vaginal approach. The overall repair success rate was 79.2% with comparable outcome in both groups-78.3% for the abdominal and 80% for the vaginal group (p=0.999). The duration of hospital stay did not differ significantly between the groups (p=0.972). Post operative complications were found in 41.4% of the abdominal group compared to none in the vaginal group (p<0.001). The complications were failed repair (20.7%) and urinary tract infection (20.7%). The mean estimated blood loss was 465.5ml in the abdominal group compared to 332.9ml for the vaginal group (p=0.303).
Conclusion: Despite the comparable surgical repair outcome of the two methods, the vaginal approach is associated with lesser blood loss and lower risk of post-operative complications. It is recommended that the vaginal route should be employed in the repair of uncomplicated midvaginal fistula unless there are other compelling reasons to the contrary.

Keywords: Mid-vaginal vesico-vaginal fistula, urinary incontinence, vaginal/abdominal surgical methods, Nigeria

INTRODUCTION
Obstetric fistula is a resultant effect of prolonged obstructed labour, an aftermath of a poorly supervised childbirth¹⁻³. It has been reported as a neglected public health issue in the world¹. Surgical expertise for managing this challenging medical condition is dwindling even in countries with many cases like Nigeria⁵. Moreover, there is also lack of dedication amongst medical personnel such as nurses, anaesthetists and other related staffs. These deficiencies have frustrated the hope of eradicating this scourge in many developing countries.

The route of repair of vesico-vaginal fistula is usually at the surgeon’s decision mostly informed by findings after examination under anaesthesia, and the background training and skills of the surgeons⁶. Urologists usually perform the fistula repair irrespective of site and size through abdominal route while most gynaecologists prefer the vaginal route⁷. Although studies have shown comparable success rate in terms of repair outcomes on the two methods of repair⁶, ⁸, ⁹ there is the need to select the best approach depending on the type, size and site of the fistula¹⁰.

Abdominal approach of repair is mostly performed under general anaesthesia to achieve optimal relaxation¹¹. However, this may be associated with many complications as well as the risk of damage to other structures such as the bowel loops, major blood vessels. Vaginal approach can be easily performed using regional or even by local infiltrative anaesthetic technique especially in well selected simple fistula¹², ¹³. The benefit of this approach includes early resumption of oral feeding, lesser risk of anaesthetic complications and a drastic reduction of cost of surgery. Inspite of these
benefits, vaginal approach is often constrained by limited operating space.

Mid-vaginal fistula is the commonest variety of obstetric vesico-vaginal fistula. In this type, the urethral sphincters are spared especially in simple/uncomplicated cases. On many occasions, pin-hole and uncomplicated fistula could be managed conservatively with appreciable success using continuous urethral catheterization for about 6-weeks\(^4\).

This study attempts to audit all cases of uncomplicated midvaginal fistulas seen at the gynaecological clinic of the University College Hospital, Ibadan over a period of seven years by comparing the outcome of repair between vaginal and abdominal approach.

**MATERIALS AND METHOD**

This was a hospital based retrospective study of patients that were managed at the University College Hospital, Ibadan on account of uncomplicated midvaginal vesico-vaginal fistula due to obstetric aetiology from January, 2000 to December, 2006. This tertiary public health institution serves as the topmost referral centre for genitourinary fistula surgery in the southwestern region of Nigeria, as well as providing leadership for capacity building and training of specialists that are interested in acquiring the skills.

The case records of women that presented with genitourinary fistula at the gynaecological clinic of the UCH were retrieved. Only those with uncomplicated mid-vaginal fistula as indicated on either the examination under anaesthesia or surgical repair operation note were selected. Where there are discrepancies in diagnosis, the surgical operative note was used for categorization of the fistula. The inclusion criteria were mid-vaginal fistula with no fibrosis or evidence of infection, lack of urethral or bladder neck involvement and not more than one previous repair attempt\(^5\). The following information were obtained from each of the selected patient's medical records; sociodemographic data, duration of urinary incontinence, number of previous repairs, presence of rectovaginal fistula, type of VVF, mode of repair (Abdominal or vaginal route), surgeon's status and specialization, presence of post operative complication, estimated blood loss and duration of hospital admission.

The entire patients that had their repair during the study period were given postoperative prophylactic antibiotics parenterally for at least 48 hours and they were followed up with oral preparation of the same antibiotics for about 5—10days. Urinary continence at discharge was used as a measure of successful repair. At least 2 follow-up visits at 4 weeks and 3 months postoperatively were checked to validate the repair outcome.

Data were obtained using a structured proforma. The statistical analysis was performed with SPSS 11 software. Bivariate analysis was performed using Chi-square and Mann Whitney U tests. Fisher's exact test was reported when expected counts in any cells on cross tabulations were less than five. The level of statistical significance was set at 5%.

**RESULTS**

Seventy one cases of midvaginal fistulae were seen during the period. The mean age of the women was 33.1 years (SD=15.2). About two thirds were married (66.2%), a quarter were unmarried (25.4%) while the remainder (8.5%) were widowed. The highest educational status was secondary. They were predominantly traders (32.4%). Others were artisans (33.8%) while about 17% were unemployed. The median duration of incontinence was 30 months. About two thirds had one previous delivery only. The abdominal route of repair was used in 29(40.8%) and vaginal in the remainder. General anaesthesia was used for all that had abdominal repair while those that had vaginal route of repair had regional anaesthesia – spinal (85.7%), epidural (4.8%) and local infiltrative in 9.6%. Two patients among those that had abdominal approach were transfused with blood. None was transfused among the vaginal approach group.

Table 1 shows the baseline characteristics, pre-operative clinical variables and outcomes of repair for the two groups of women. Women in the abdominal group were significantly older (p=0.012) and had a significantly higher number of previous deliveries (p<0.001) than those who had vaginal repair. The groups were not significantly different concerning duration of incontinence though the abdominal group appeared to present earlier (p=0.503). Fistula sizes were similar between the groups with mean diameters of 4.6cm and 3.5cm for the abdominal and vaginal routes respectively (p=0.126). Only vaginal repair group had associated rectovaginal fistula (RVF) in 14.3% of them (p= 0.075). None of the women in the abdominal group had a previous repair compared to about 28.6% of those in the vaginal group (p=0.005). All the women in the abdominal group had general anaesthesia compared to 20.7% of those in the other group (p<0.001).

The overall success rate was 79.2% which was almost equal in both groups-78.3% for the abdominal route and 80% for the vaginal group (p=0.999). The duration of hospital stay did not differ significantly between
Post operative complications were found in 41.4% of the abdominal group compared to none in the vaginal group (p<0.001). The complications were failed repair (20.7%) and urinary tract infection (20.7%). The mean estimated blood loss was 465.5ml in the abdominal group compared to 332.9ml for the vaginal group though the median blood loss was the same in both groups (p=0.303).

**DISCUSSION**

Eradication of obstetric fistulae has remained a herculean task especially in the area of surgical repair. Use of simple effective surgical and anaesthetic methods will facilitate better access to care for fistula victim that are often embroil with poverty and social annihilation.

In this study, the median duration of urinary incontinence prior to presentation and mean diameter of the fistula size were similar in both groups. These similarities offers opportunity for objective comparism as both factors have direct impact on outcome of repair. Longer duration of urinary incontinence predisposes to infection and subsequent tissue fibrosis that may result in poor healing. Also, larger fistulae are usually accompanied by poorer outcome due to difficulty in tissue mobilization during surgical repair. The women managed differed significantly in median age at presentation, parity, methods of anaesthesia and previous repair attempt. In addition, there is associated rectovaginal fistula among those that had vaginal repair. Of all the observed differences among patients managed in both groups, presence of rectovaginal fistula and previous repair attempt has been shown to have significant influence on the outcome of repair.

RVF predisposes to fecal soilage and subsequent

Table 1: Baseline characteristics and outcomes by route of repair

*Mann Whitney U test used for comparison
**Fisher’s exact test
+ Chi square test used as significance test

<table>
<thead>
<tr>
<th>Characteristics and Preoperative clinical variables</th>
<th>Abdominal (n=29)</th>
<th>Vaginal (n=42)</th>
<th>Test statistic</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years) (Lowest – Highest)</td>
<td>31(20-80)</td>
<td>27(22-30)</td>
<td>396*</td>
<td>0.012</td>
</tr>
<tr>
<td>Median number of deliveries (range)</td>
<td>2(6)</td>
<td>1(0)</td>
<td>252*</td>
<td>0.000</td>
</tr>
<tr>
<td>Median duration of incontinence in months (range)</td>
<td>17(352)</td>
<td>42(70.5)</td>
<td>552*</td>
<td>0.503</td>
</tr>
<tr>
<td>Mean fistula size (cm) (median)</td>
<td>4.5(4.0)</td>
<td>3.5(4.0)</td>
<td>264*</td>
<td>0.126</td>
</tr>
<tr>
<td>General anaesthesia (%)</td>
<td>100.0</td>
<td>20.7</td>
<td>49.27*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Associated Rectovaginal fistula (%)</td>
<td>0.0</td>
<td>14.3</td>
<td>0.075(FET)</td>
<td></td>
</tr>
<tr>
<td>Previous repair (%)</td>
<td>0.0</td>
<td>28.6</td>
<td>0.005(FET)</td>
<td></td>
</tr>
</tbody>
</table>

| Outcomes                                           |               |               |                |     |
| Mean estimated blood loss (median)                 | 465.5(300)    | 332.9(300)    | 522*           | 0.303 |
| Median duration of hospital admission in days (range) | 25(15)        | 24(44)        | 606*           | 0.972 |
| Post operative complications (%)                   | 41.4          | 0.0           | <0.001(FET)    |     |
| Success rate (%)                                   | 78.3          | 80.0          | 0.999(FET)     |     |

the groups (p=0.972). Post operative complications were found in 41.4% of the abdominal group compared to none in the vaginal group (p<0.001). The complications were failed repair (20.7%) and urinary tract infection (20.7%). The mean estimated blood loss was 465.5ml in the abdominal group compared to 332.9ml for the vaginal group though the median blood loss was the same in both groups (p=0.303).
infection of the operation site. Temporary fecal diversion with colostomy and two-stage repair is often routinely performed to prevent this complication. Recently, Ojengbede et al. have demonstrated that one stage repair of combined fistula is feasible when appropriate precautionary measures such as adequate bowel preparation; rectal washout and surgical expertise are employed. The pattern of repair – whether one or two stage, were not considered for analysis in this study. The number of repair attempts is one of the key determinants of the genitourinary fistula surgery outcome because of the associated fibrosis from previous healing. In this study, about 14.3% and 28.6% of women with vaginal repair had associated RVF and previous repair attempt respectively. Despite these limitations, comparable successful outcome were recorded. One factor that may confound this observation is the skill and experience of the surgeons which will be difficult to objectively analyse.

Of recent, fistula experts are making spirited efforts in ensuring accessible and affordable treatments to victims without compromising both ethical and surgical standards. Use of simple, effective and cheap anaesthesia is one of such strategies that have drastically cut down the cost of care. All women that had abdominal approach were offered general anaesthesia during the study period. This anaesthetic technique would have added to the financial burden. Regional anaesthesia such as subarachnoid and epidural block could be used but, none among those in abdominal repair had these methods. All women among the vaginal repair group had all forms of regional anaesthesia including local infiltrative technique as an anaesthetic agent.

On the outcome of repair, there were comparable average surgical blood loss, median duration of hospital stay and post operative incontinence between the two methods of repair. In spite of these similarities, women that had abdominal repair bled more in excess of about 130ml and stayed longer by a day compared to those with vaginal method. The differential blood loss may appear insignificant in well nourished individual but, such loss could adversely affect fistula patients that are usually poorly fed and anaemic. In addition, two women had blood transfusion in the abdominal approach group. They are therefore at risk of transfusion reactions and infections. Only women with abdominal repair suffered post operative complications. The pattern of complications was urinary tract infection and failed repair. The higher infection rate may be due to extensive bladder dissection and mobilization of surrounding tissues; this may have affected the tonicity of the muscle after surgery. The failed repair attempt may not necessarily be as a result of the route of repair but may be due to other confounding issues such sub-clinical infection, skill of the surgeon and difficulty tissue mobilization at surgery.

From this audit, one can argue that choice of repair route does not have significant effect on the overall success of the outcome as there was no appreciable difference. Overall, 78.3 percent and 80.0 percent success were recorded in abdominal and vaginal route of repair.

In conclusion, vaginal repair of mid-vaginal VVF is associated with lesser blood loss and post operative complications despite the compared characteristics of patients managed. Use of regional anaesthesia including local infiltrative technique provides ray of hope for fistula victims that often suffer delayed care from large number of patients awaiting surgery as this method could be performed by either the surgeon or other accompanying health care personnel especially in centres with dearth of capacity. It is therefore recommended that as much as feasible, vaginal route should be employed in the repair of uncomplicated midvaginal fistula unless there are other compelling reasons to the contrary.

REFERENCES


