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Building Sustainable Capacity for Disease Diagnosis in Sub-Saharan Africa: Case Studies of Cooperation in Diagnostic Pathology

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1. Introduction

One of the most important outcomes of globalization's complex and debated processes is the possibility of promoting and upgrading services in geographically remote areas. Globalization yields the easiest means of transportation and communication, which makes networking a relatively simple process. Moreover, innovative sound technologies, such as tele-consultation, provide these networks with a solid base for continuation and further buildup. These possibilities apply to the field of Medicine in general, and Pathology in particular. These new opportunities are very promising in regard to the endeavor of building sustainable capacities for disease diagnosis in sub-Saharan Africa.

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In this chapter we describe cases of cooperation in the field of diagnostic pathology in sub-Saharan Africa that exemplify benefits from globalization. In these regards we believe that networking of sub-Saharan African institutions with biomedical centers and associations of pathologists in developed countries could significantly improve the current situation in many sub-Saharan African countries. However, to gain maximum benefits from globalization-related activities (networking/tele-consultation, etc.), there is a fundamental need for strongly committed contexts both in sub-Saharan African countries and in developed countries.

Pathology plays a pivotal role in diagnosis, staging and management of disease. The lack of adequate pathology services undermines the ability to rationally address health care needs and patient treatment based on evidence-based knowledge (Gray & Carter 1997; Greene et al. 2002; Benediktsson et al. 2007). However, pathology is often perceived as a peripheral and ancillary biomedical specialty, which, under the pressure of limited resources, may be sacrificed to the benefit of needs regarded as more urgent (Awadelkarim et al. 2010b). Such wrong perception may account for the scarcity of pathology services in sub-Saharan Africa and for the fact that such services, when provided, are often below acceptable standards (Hutt & Spencer 1982; Gray & Carter 1997; Awadelkarim et al. 2010b).

The extreme shortage of pathologists and laboratory technicians in sub-Saharan Africa is a major issue (Gray & Carter 1997; Awadelkarim et al. 2010b): for example, in 2007 Uganda had 18 pathologists for a population of 28 millions, Tanzania 15 for 38 millions, Sudan 51 for 40 millions (Benediktsson et al. 2007; Awadelkarim et al. 2010b). Emigration further compounds this problem: in fact, the necessity of training abroad, the awareness of the difficulties in applying newly-acquired skills back home, and the experience of the Western job market leads to a "brain-drain" from developing to developed countries (Garrett 2007). This depletes the human resources and the dissemination of knowledge.

Major challenges that need to be faced to improve pathology in sub-Saharan Africa include the geographic distances, which require logistic systems for sending appropriately annotated specimens from peripheral hospitals to centralized laboratories; the high temperatures (often above 45°C) which result in the difficult use of paraffin wax, stains, and chemicals; the generally inadequate access to electricity services, with consequent frequent and extended outages; the dust and very poor maintenance, that compromise equipment and samples; the absence or inadequacy of standard operative procedures (Vacca 1985; Dafallah et al. 2005; IMF Survey online 2008 ; Bancroft & Gamble 2008).

The implementation of new pathology activities in Africa must find a strong local commitment and should rely on strategies that combine economical sustainability in time with realistic compromises between costly "gold standard techniques" and less expensive alternatives, that could be more suitable to the environmental, infrastructural and personnel limitations. A cost-effective approach is mandatory in limited resource contexts and research should be oriented to develop innovative and less expensive diagnostic methods. To exemplify the feasibility of such approach it is worth to cite the article entitled "The poor man's cell block," a contribution from New Zealand describing a simple method to obtain a cell block (i.e., an inclusion for histology based on cell samples) that links the easy and widespread use of fine needle aspiration cytology to the power of detailed histological visualization (Leung & Bedard 1993; Mayall & Darlington 2010). The method is interesting also because it substitutes formalin with iso-propyl alcohol in fixation. Formalin is safe only in presence of adequate and perfectly efficient aspiration devices, generally not available in pathology laboratories operating in contexts with limited resources. The use of alternative fixatives is a reasonable and cost-effective alternative to expensive aspiration hoods, which need regular servicing and substitution, and proper disposal of costly filter units.

The expertise required for African pathologists must comprise infectious diseases, including not only major global diseases such as malaria, AIDS and tuberculosis, but also neglected endemic tropical diseases, one of the key areas of health concern for Africa, as these diseases, in principle preventable and treatable, result in life-long physical pain and social stigma when overlooked (Muela Ribera et al. 2009). However, while this “traditional” infectious focus of African pathology remains very important, the need for expert cancer pathologists is rapidly growing, in parallel with the increasing incidence of cancer in Africa. According to the African-Oxford Consortium and World Health Organization, 15 million new cases of cancer worldwide are projected by 2020, and 70% of these will be in developing countries (Lingwood et al. 2008), with special problems in Africa (Morris 2003; Awadelkarim et al. 2010a).

2. Neglected tropical diseases

The World Health Organization (WHO) is currently focusing on 17 neglected tropical diseases (http://www.who.int/neglected_diseases/diseases/en/): Buruli ulcer, Chagas disease (American trypanosomiasis), cysticercosis, dengue/dengue haemorrhagic fever, dracunculiasis (guinea-worm disease), echinococcosis, fascioliasis, African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, rabies, schistosomiasis, soil transmitted helminthiasis, trachoma and yaws. These diseases, to which children are most vulnerable, affect an estimated one billion people, primarily among the poor populations in Africa, and are mostly attributable to well-known environmental factors, notably unsafe water, poor housing and poor sanitation (Stein et al. 2007). Programs aimed at controlling or eliminating these endemic diseases have come together in the Neglected Tropical Disease Coalition, which provides a unique opportunity for collaborative advocacy activities in industrialized countries while member organizations also explore coordination or integration of disease treatment and prevention in endemic countries (<http://www.neglectedtropicaldiseases.org/about.html>).

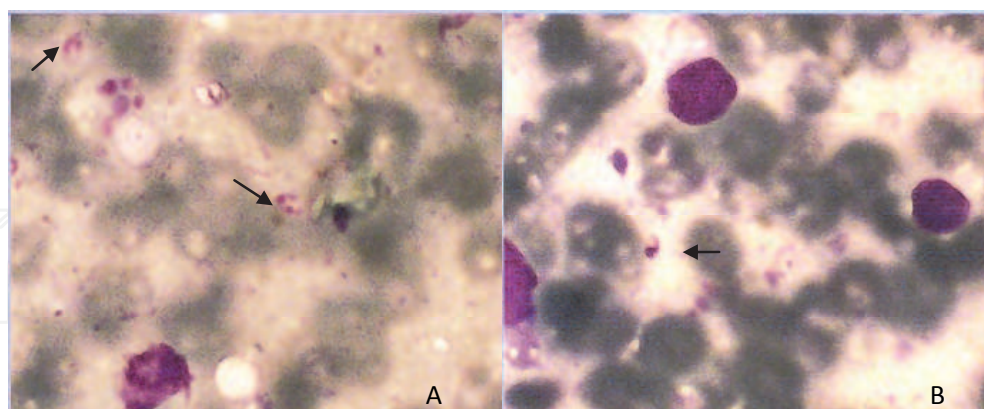


Fig. 1. Lymph node puncture stained with Giemsa. Leishman–Donovan bodies are seen (arrows). Case history: 17 years-old boy complaining of fever, fatigability and loss of weight. Clinical examination revealed a febrile anaemic patient with splenomegaly and enlarged cervical, axillary and groin lymph nodes. Differential diagnosis included acute leukemia, infectious mononucleosis and kala-azar. Fine needle aspiration was performed on one of the cervical lymph nodes. Cytology showed bloody background with mainly lymphocytes and few extracellular Leishman–Donovan bodies. Diagnosis of kala-azar (visceral leishmaniasis) was made.

Endemic tropical diseases are tied to specific geographic and environmental conditions and carriers do not travel easily. Therefore these diseases are not perceived as a threat to developed societies and are neglected in most western pathology training programs. This results in a global lack of diagnostic capabilities, which negatively reflects on African health and on necessary finalized research. Thus, there is a need to introduce endemic diseases in the pathology training programs of developed countries. This could be done by networking with clinical centers and Universities in sub-Saharan Africa, and it could contribute to the global development of pathology training. Figures 1-4 exemplify educational cases of neglected tropical diseases from the files of the Pathology Department of Gezira University, Wad Medani, Sudan.

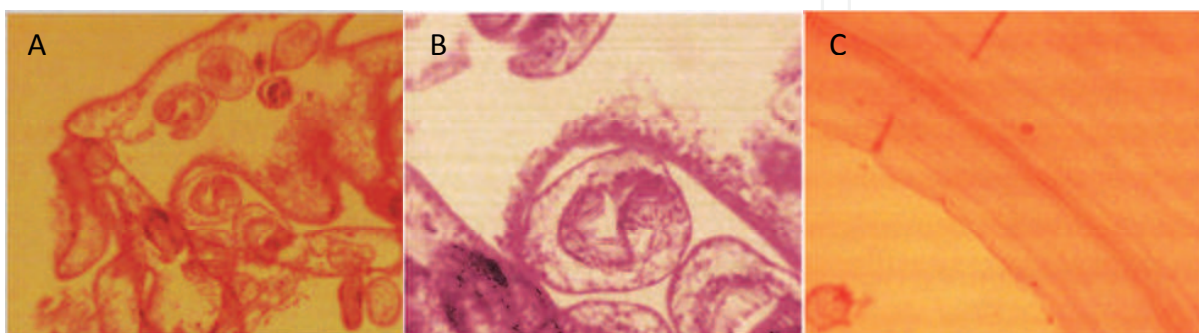


Fig. 2. Breast hydatid cyst. Case history: housewife aged 35 years, who complained of a right breast lump increasing gradually in size for the last two years, with mild pain. Local examination revealed a 5 cm cystic lump, which was totally excised. Macroscopically, the lesion consisted in a 5.5 cm diameter fibro-fatty tissue mass containing a thick-walled 4.3 cm cyst. Microscopic examination shows a cyst containing scolices of *Echinococcus granulosus* and a thick laminated (brood) capsule, features typical of hydatid cyst (A & B: scolices and inner membrane, C: laminated capsule, H&E stain).

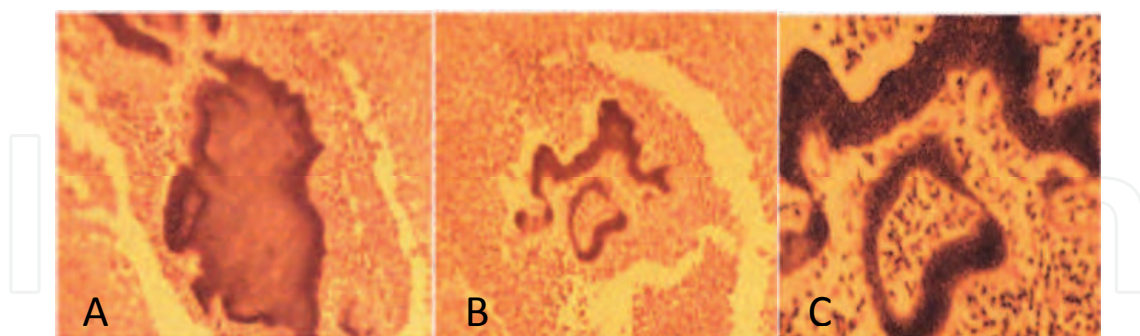


Fig. 3. Yellow Madura. Case history: 17 years-old female complaining of right leg swelling present for 5 years, with recent discharge of pus containing yellowish material, but no significant pain. Clinical examination showed right leg swelling, mainly around the ankle joint and involving the heel. Operated under general anaesthesia using tourniquet, it was found that the lesion involved the tendons, being very close to bone. Macroscopic examination showed a 7.0 cm diameter irregular fibro-fatty tissue mass containing pus with yellowish granules. Microscopic analysis shows chronic inflammation and fibrosis, with foci of micro-abscesses containing structure-less fungal elements. These features are consistent with yellow Madura (A, B & C, sections from left leg lesion, H&E stain).

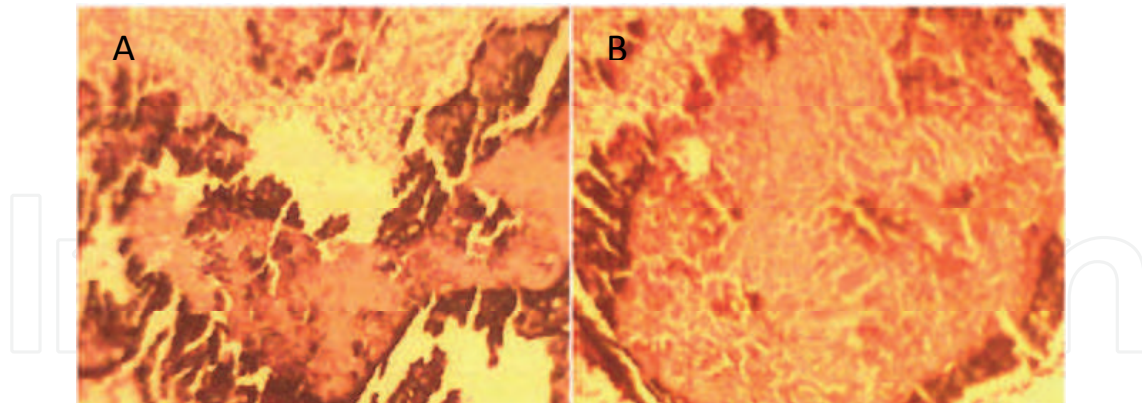


Fig. 4. Grains of black Madura. Case history: 29-years old man complaining of a painless foot swelling for the last 2.5 years, with no documented history of trauma or injury. Examination showed a well-circumscribed, partially mobile, non-tender 3.5 cm swelling in the sole of the left foot, with normal-appearing overlying skin and no discharging sinuses. The lesion was excised under general anesthesia. Differential clinical diagnosis included fibroma, giant cell tumor or Madura. Macroscopic examination showed a 4.0 cm well-encapsulated, firm mass. Sectioning revealed whitish tissue studded with necrotic areas containing small black granules. Microscopic examination showed chronic inflammation with granulomas surrounding dark-brown fungal elements. The features were consistent with *Madurella mycetomi* (black madura) infection. (A & B, views of sections from mass, H&E stain).

2.1 A North-South intervention against a neglected tropical disease: Buruli ulcer in Benin

An enigmatic infectious disease, Buruli ulcer (children leprosy), is the subject of a model North-South pathology intervention in Benin, within the framework of the WHO Buruli ulcer program. Buruli ulcer is a highly destructive necrotizing skin disease, usually with insidious painless onset, which occurs in tropical and subtropical areas of West Africa and South-East Australia, with increasing geographical spread (Zavattaro et al. 2010). More than 50% of the patients are below 15 years age. The disease is caused by *Mycobacterium ulcerans* (Connor et al. 1976), an opportunistic pathogen that grows at low temperature (30 to 35°C) in a rarefied oxygen ambience and produces pathologic effects through a plasmid-encoded macrolide toxin (mycolactone). The lesions involve primarily the deep dermis and the subcutaneous tissue, manifesting under various clinical forms, the most dramatic being large ulcerations that may reach the bone (Leigheb et al. 2008) (Figures 5, 6).

The classic treatment of Buruli ulcer relies on bi-antibiotic therapy (streptomycine/rifampicine), followed by surgical excision of the necrotic tissues and skin graft (Nienhuis et al. 2010). Hyperbaric oxygen therapy (Figure 6), even if not able to prevent germ growth, is an important adjuvant. It protects against over-infections after excision of necrotic tissues, it stimulates neo-vascularization with improvement of grafting, and it accelerates wound healing, reducing the risk of hypertrophic scars, which result in permanent deformities and loss of joint functions.

'Oxygen for Life' is an ongoing project in Benin involving an Italian team lead by the Service of Anatomic Pathology and Cytopathology of the S. Pio X Clinic of Milan and other Italian Institutions, supported by important and stable private donations, in connection with the WHO's Buruli ulcer program (<http://www.who.int/buruli/en/>). This initiative currently provides expertise in pathologic diagnosis and medical/surgical treatment of Buruli ulcer, as well as the provision and maintenance of a multi-place hyperbaric oxygen chamber at the *Centre de Dépistage et de Traitement de l'Ulcère de Buruli* in Alladà, Benin, a facility unique in Africa (Figures 7). This program resulted in a significant improvement of clinical end points and quality of life for Buruli ulcer patients in Benin.



Fig. 5. Buruli ulcer before treatment.



Fig. 6. The same case after combined antibiotic and hyperbaric oxygen treatment.

The project involves multiple areas of expertise, including a specialized engineer responsible for the maintenance of the oxygen chamber already in place, and for the installation of a second one. A histopathology lab was also implemented *ex novo*, combined with a telepathology connection, which upgrades the diagnostic capabilities of the African team, as discussed further on. Meanwhile, a research project was started with the aim of understanding the natural history of *M. ulcerans*, with special regard to its possible diffusion from animal reservoirs.

Transmission modes are still uncertain, but epidemiological evidences indicate that inter-human contagion is rare. Rather than pointing to a single, specific vector, the available data suggest a key role for environmental factors, with a possible natural reservoir of the pathogen in aquatic insects, particularly of the *Naucoridae* and *Belostomatidae* families (Portaels et al. 1999). To verify this hypothesis, zoological samples collected in the endemic areas of Alladà and Lalo in Benin were analyzed with sensitive molecular techniques (polymerase chain reaction, PCR) for microbial DNA. More than 2,500 samples of aquatic insects (mosquitoes, coleoptera, larval Odonata, water-scorpions, etc.), as well as amphibians (frogs and tadpoles), mollusks, fish, shellfish, algae and samples of spring water, slime, and Akponé (Zé) water plants, were tested in cooperation with the Microbiology Laboratory of the University of Sassari, Italy. Only a few insects of the family *Naucoridae* gave positive results.

The “Oxygen for Life” project is contributing to the formation of a team of African pathologists, physicians and surgeons specialized in Buruli ulcer, and is bringing this forgotten disease to international attention, stimulating also specific research. It provides an illuminating example of globalization in the fight against neglected endemic tropical diseases in Africa.



Fig. 7. The four place hyperbaric oxygen chamber functioning at the *Centre de Dépistage et de Traitement de l'Ulçère de Buruli* (CDTUB) in Alladà, Benin.

3. Need of pathology for the development of African oncology

African governments and development agencies have thus far focused their attention on communicable diseases, and maternal and child mortality (World Health Organization 2004; Lingwood et al. 2008). However, these older health problems coexist now with new ones, in particular HIV/AIDS and cancer, which are closely connected and rapidly progressing. The importance of infections as a major cancer risk factor in Africa is clearly evidenced by the fact that as many as 36% of the cancer cases in the African continent are infection-related, which is double the world average (Parkin et al. 2008).

The WHO forecasts a dramatic increase of incidence of cancer in Africa in the next decades and the necessity to implement efficient oncology services. However, accurate cancer data are difficult to obtain because registries cover only 11% of the African population (Porter 2008), and the quality of information is poor because of the severe shortcomings in pathologic diagnosis (Parkin et al. 2003; Parkin 2006; Awadelkarim et al. 2010a; Awadelkarim et al. 2010b). Mortality statistics for cancer are also inadequate; since 1995, only three African countries (Mauritius, Egypt, and South Africa) contributed to the cancer mortality database. However, even in South Africa, death registrations for cancer are estimated to be incomplete (Parkin et al. 2003). Nonetheless, about 650,000 new cases of cancer were estimated to have occurred in Africa in 2002, 530,000 of which in sub-Saharan countries (Ferlay et al. 2004). Interestingly, cancer incidence and mortality seem to have risen before the spread of the current HIV/AIDS epidemics (Bulatao 2006).

As mentioned earlier, while cancer treatments must be adapted to fit local health conditions with cost-effective protocols, any treatment must be based on sound histological diagnosis (Greene et al. 2002), but this is largely unfeasible due to the dramatic shortage of histopathology and cytopathology services.

3.1 Carcinoma of the uterine cervix: Need of novel pathology-based approaches to prevention

The lack of pathology services is felt particularly in the area of cancer prevention in women, as exemplified by carcinoma of the uterine cervix. With an estimated incidence of 30-40 per 10^5 females, carcinoma of the uterine cervix is the most common cancer of women in sub-Saharan Africa (Parkin et al. 2008). It is well known that the agents responsible for this cancer are human papilloma viruses (HPVs) (zur Hausen 2009) and that this cancer can be effectively cured when treated at early stages, as it mostly occurs in the developed world. However, in Africa the vast majority of the affected patients seen in hospitals have advanced to incurable disease at stages III or IV (Hamad 2006; Sitas et al. 2008). Another problem linked to this cancer in Africa is that HIV/AIDS represents a risk factor for persistent infection with cancer-related HPVs (Palefsky 2009; Singh et al. 2009).

The primary approach for cervical cancer in developed countries is prevention by organized population screening. In sub-Saharan Africa, the lack of infrastructures, trained personnel and funds make large-scale cytology screening programs unfeasible. Presently, diagnosis and treatment of cervical cancer are possible only in few organized centers, mainly in capital cities. Nonetheless, recent technological developments in cervical cancer screening could open a window of new opportunity for sub-Saharan African countries. In fact, in countries with established cytology prevention programs, HPV DNA testing is becoming the most attractive option for primary screening (Meijer et al. 2009) and there is a tendency to recur to it as the sole screening modality, with cytology reserved for triage of HPV-positive women.

Furthermore, the new molecular tests allow to detect not only HPV DNA, but also the full-length E6-E7 transcripts of the high-risk viruses that are associated with lesions which could progress to cancer (Cuzick et al. 2008; Zappacosta & Rosini 2008). Therefore, established cytology-based programs are gradually moving towards a greater use of HPV DNA testing to improve efficacy and safely lengthen screening intervals. The higher sensitivity of HPV DNA testing compared to cytology argues strongly for using HPV DNA testing as the primary screening test in newly implemented programs in Africa.

In low resource settings, an interesting method that could be used for screening is visual uterine cervix inspection with acetic acid (Cuzick et al. 2008; Sankaranarayanan et al. 2008). This inexpensive method can be carried out using modest equipment and widely available consumables, without laboratory infrastructures. The sensitivity in the detection of high-grade precursor lesions and invasive cervical cancer has varied from 49 to 96% and the specificity from 49 to 98%, being significantly lower in human immunodeficiency virus (HIV)-positive women, but the possibility to use HPV-DNA test to detect high risk viruses could complement this test (Cuzick et al. 2008). This would reduce reliance on cytology, too expensive and difficult to implement in Africa for lack of facilities and trained personnel (Cuzick et al. 2008).

Regardless of the tests used, screening must be linked to treatment to ensure program effectiveness. An option is a “screen and treat” algorithm, in which any suspicious lesion is referred for cryotherapy or loop electrosurgical excision, safe, effective and inexpensive outpatient methods used for treatment of cervical pre-cancer (Cuzick et al. 2008). After initial screening by HPV DNA testing of all women, those resulting HPV-negative could be recalled after 5-10 years; while those resulting HPV-positive could be visually-inspected, followed by immediate treatment. In women negative by visual inspection, the screening process could be repeated after 12-24 months. This approach could be combined with a mother-daughter approach for preventive vaccination. The HPV vaccine, now largely used in developed countries, is far from being available in Africa, due to costs and other social and organizational factors; however, it could be an effective tool to reduce health inequality for African women (Pollack & Tsu 2005; Tsu & Pollack 2005). In the aforementioned combined approach, daughters could be vaccinated while mothers are screened or treated.

3.2 Development of diagnostic capabilities in cancer pathology through North-South cooperation: St. Mary's Hospital Lacor in Gulu, Uganda, and the Association *Patologi Oltre Frontiera*

In Uganda, as in other sub-Saharan African countries, cancer appears to be steadily more important as a cause of disease and mortality (Table 1). As expected, the most prevalent cancers are associated with viruses, such as the human papilloma virus (carcinoma of the uterine cervix), EBV and HIV (lymphoma), HIV/AIDS and KS-associated Herpes virus/Human Herpes virus 8 “KSHV/HHV-8” (Kaposi sarcoma) (Table 2).

The Uganda Health Sector Strategic Plan III 2010/11-2014/15 acknowledges that “non-communicable diseases and their risk factors are increasing in low income countries including Uganda.” Already in 2006, the Ministry of Health established a program for the prevention and control of non-communicable diseases and, in collaboration with stakeholders, initiated the process of conducting a baseline study, yet to be completed, on risk factors and magnitude of such diseases. Major challenges in the control of chronic diseases in Uganda are the lack of local data, the inadequate capacity of the health system to address them, and the high cost of medicines and supplies.

Uganda has four medical schools; the oldest of these is Makerere University in Kampala, where in 1958 Denis Burkitt first reported on the lymphoma later entitled to his name (Burkitt 1958).

Uganda	Male	Female	Both sexes
Population (thousands)	15849	15807	31656
Number of new cancer cases (thousands)	11,8	15,3	27,1
Age-standardised rate (W)	156,9	186,8	171,9
Risk of getting cancer before age 75 (%)	16,4	19	17,8
Number of cancer deaths (thousands)	9,9	11,4	21,3
Age-standardized rate (W)	135	143	139,3
Risk of dying from cancer before age 75 (%)	14,1	15,5	14,8

Source GLOBOCAN 2008 (IARC), Section of Cancer Information (8/8/2010)

Table 1. Cancer in Uganda

Uganda	Male	Female	Both sexes
1	Kaposi sarcoma	Cervix uteri	Kaposi sarcoma
2	Prostate	Kaposi sarcoma	Cervix uteri
3	Oesophagus	Breast	Breast
4	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma
5	Liver	Stomach	Prostate

Source GLOBOCAN 2008 (IARC), Section of Cancer Information (8/8/2010)

Table 2. Five most frequent cancers in Uganda

The Uganda Cancer Institute was established at Mulago Hospital in 1967 as the teaching hospital of Makerere University. The other government Medical Schools are Mbarara University of Science & Technology (since 1989) and Gulu University (since 2001), while Kampala International University (since 2001) is a private institution. However, it is possible to obtain a Master in Pathology only at Makerere. Cytopathological or histopathological diagnosis is essential for cancer treatment, and this is especially important for a country with limited resources such as Uganda, as it helps to avoid unnecessary and unhelpful therapies, therefore enabling a better use of resources.

St. Mary's Lacor Hospital, located about 6 km west of Gulu in North Uganda (Figure 8), is a private, non-profit, catholic-based institution founded in 1959 by the Combonian Missionaries and since then it has had a steady and continuous development. Lacor is one of the 21 government-designated national sentinel surveillance sites for monitoring trends of HIV/AIDS epidemic in Uganda. It is registered with the National Board for Non-

Governmental Organizations, it is accredited to the Uganda Catholic Medical Bureau and it provides all the major components of the Uganda Minimum Health Care Package, offering inpatient, outpatient and community-based services. It has adequate facilities and infrastructures, constant availability of electricity and water, and a well-trained staff of about 580 people (of which 35 MDs and 200 nurses). It includes a 470-bed hospital, 3 peripheral health centers (Opit, Amuru and Pabbo), and a teaching site with a Nurse Training School, a School of Laboratory Assistants and other training programs. It serves also as a teaching site for the Gulu University Medical School. The hospital receives patients from the Gulu District, other parts of North Uganda and South Sudan, serving on average 600 inpatients plus their attendants, and 500 outpatients daily.



Fig. 8. St. Mary's Hospital Lacor is located near Gulu in North Uganda. Gulu is indicated by star.

At Lacor, before 2008 the histopathological specimens sampled by surgeons (about 1600/year) were processed manually in a small histopathology laboratory by a technologist and the stained slides were sent to the Pathology Department of Mulago University in Kampala, which sent back the diagnostic reports by FAX. It took more than a month to get a diagnosis. The turnaround time and accuracy of pathological diagnosis was unsatisfactory, with profound impact on patient management and ultimate outcome. Patients were often lost to treatment before diagnosis. Lack of accurate diagnosis also impaired research projects.

These problems prompted the hospital direction to contact the Italian NGO *Associazione Patologi Oltre Frontiera* (Pathologists Beyond Borders, APOF), a non-governmental association of Italian pathologists founded in 1999 with the aim of realizing projects for developing pathological anatomy and cancer diagnostics in the South of the world. Based on its experience in creating pathology services in developing countries, APOF was charged with the task of establishing a histopathological diagnostic service at Lacor Hospital.

The project was launched in July 2008 thanks to a grant for laboratory equipment from the Province of Bolzano, Italy, and it aims to create a functioning pathology service inside the hospital compound, staffed with a local pathologist. The Italian Ministry of Foreign Affairs provided up to 2010 contracts for pathologists who stayed for at least 4 months, while volunteer pathologists who stay a month have travel expenses and accommodation paid by Lacor Hospital. Since the beginnings, the diagnostic service has been secured by the continuous presence of volunteer pathologists, with two local technologists. This is going to continue until the local medical officer designated to become staff pathologist will have completed training. The laboratory can perform not only basic stains as H&E, but also PAS, Giemsa, Ziehl-Neelsen and Papanicolaou for vaginal smears and cytology. Basic immunostaining is also possible. The microscope has a digital camera and is linked to a computer for the acquisition of images. A second computer has software for basic data collection and writing/printing reports. The laboratory is "twinned" with specialized centers in Italy, mainly the Pathology Department at the University of Siena, and can get "on line" help.

Since 2008 the number of histopathology and cytology exams has been steadily increasing (2008: 254 for cytology, 1280 for histology; 2009: 453 for cytology, 1575 for histology; 2010: 1052 for cytology, 1930 for histology) and data from the pediatric ward show improved diagnosis of childhood tumors, dependent on the introduction of a limited panel of immunohistochemical stains for lymphoproliferative diseases and for the discrimination of hematological malignancies versus other neoplastic or even non-neoplastic diseases.

Integral part of the APOF program at Lacor is to raise the awareness of the medical and nursing staff of the new service and of its diagnostic and scientific possibilities. The presence of a functioning Pathology Laboratory enables the Lacor Hospital to participate in scientific studies such as EMBLEM (Epidemiology of Burkitt Lymphoma in East African Children or Minors, <http://clinicaltrials.gov/ct2/show/NCT01196520>) and the INCTR study on Burkitt lymphoma (<http://inctr-news.wikidot.com/inctr0306>).

This is important, as Burkitt lymphoma is one of the frequent childhood cancers in Uganda. Both studies enroll patients who benefit in many ways, for instance in terms of free treatment and support extended to their families. The establishment of a Pathology Service also allowed Lacor Hospital to start a screening program for cervical cancer, directed to women attending the antenatal and AIDS outpatient clinics, critical because cervical cancer is one of the tumors developing in AIDS (Bellan et al. 2003; Parham et al. 2006). The prevalence of HIV infection in adults in Uganda is about 6.7%, and about 57% of all adults living with HIV are women; thus it is of the highest importance that these women are screened to prevent cervical cancer, a concept clearly stated in the Uganda Health Sector Strategic Plan III 2010/11-2014/15. Screening can only be successful when diagnosis is made in a short time, as delays often result in loss of the patient to follow up.

4. Situation analysis of pathology training and services in Sudan

Sudan provides an example for the challenges that face the development of pathology in sub-Saharan Africa. Historically, pathology services began with the Wellcome Tropical Research Laboratories in 1903, followed by the Stack Medical Research Laboratories, established by the British General Governor, Sir Lee Stack. This is now the National Health Laboratory of Sudan. It was the only laboratory providing histopathology services for Sudan until 1978, and reports were sent by telegraph to all the Sudanese states. Gradually

some regional histopathology laboratories were established, the first of them built by the University of Gezira in 1978, as reviewed by Awadelkarim and co-authors (Awadelkarim et al. 2010b).

Currently, all histopathology services in Sudan are sustained by only 51 pathologists, 40 (78.4%) of whom working mostly in Khartoum. Three pathologists (5.9%) service the Northern States, two (3.9%) Western Sudan, two (3.9%) the western part of Central Sudan, two (3.9%) Eastern Sudan and three (5.9%) Gezira State, the most populated area of Central Sudan, servicing about four million people (10% of the total population of Sudan, spread across 26,075 km²). Pathology services are also provided by private laboratories in Khartoum and in few other main towns, e.g., Wad Medani in Gezira State.

Up until 1980, most pathologists were trained in Western countries, mainly in the UK. This important training opportunity was unfortunately interrupted for political and economic reasons. Currently, there are only two postgraduate clinical pathology programs for medical officers in Sudan, one at the University of Khartoum (since 1980), and the other at the University of Gezira (since 1993). Both are four-year MD programs.

During 2009, there were 40 clinical pathology students enrolled at the University of Khartoum and 12 at the University of Gezira. In both programs, the first two years comprise Part 1, with theoretical general teaching in the four major branches of pathology (i.e., chemical pathology, microbiology, parasitology and entomology), hematology and blood transfusion, and histopathology and cytopathology. Students also rotate periodically in major laboratories. In the second two years (Part 2), students choose two subjects, which they study in detail, with regular seminar and journal club attendance. The main training in Part 2 is practical work in recognized laboratories under the supervision of experienced pathologists. A research project is required from each student. About 50% of the students take histopathology as their major subject. This four-year course leads to specialist registration in the Sudan Medical Council register.

Most of the graduates prefer to work in the capital, Khartoum. The Federal Ministry of Health has an agreement with Malaysia, where about 40 candidates are trained to MSc level in hematology, histopathology, and microbiology. Candidates undergo a minimum of three-month performance assessment by two consultants when they return to Sudan before specialist registration. In Sudan there are 19 faculties of medical laboratory sciences. The programs are generally of four years; they include a three-year general course in medical laboratory technology and basic medical sciences, followed by a fourth year for specialization in one of the above mentioned four major branches of pathology, leading to registration as a technologist in the Sudan Health Profession Council register.

Laboratory technicians and technologists mostly practice independently, with no supervision from a pathology-specialized MD, except in histopathology and cytopathology. According to the Sudanese Ministry of Higher Education and Scientific Research (<http://www.mohe.gov.sd/content/statistics.htm>), the Sudanese medical laboratory schools had 4,505 undergraduate students in 2007–2008. In the same year, 837 medical candidates graduated in medical laboratory technology. Thus, an effort towards formation in pathology and medical technology is currently being made.

It is difficult to obtain data on the number of pathology specimens examined in Sudan, due to the fragmented nature of the services. A rough estimation ranges from 30 to 40 thousand specimens per year. Many laboratories use semiautomatic tissue processors and produce formalin-fixed paraffin-embedded blocks and routine sections stained with hematoxylin and eosin. A few laboratories add some special stains, like PAS, Alcian Blue, reticulin and Van

Gieson, especially for liver, kidney, and gastrointestinal biopsies. Immunohistochemistry services are provided by three laboratories and cytogenetic studies by one laboratory, all located in Khartoum, the capital city of Sudan.

However, almost all the pathology laboratories operating in Sudan have no written standard operative procedures covering quality control and quality assurance policies, and no strict measures against biologic risk for technologists and pathologists. Frequently the specimens are received unfixed, often being supplied in saline, and sometimes in absolute alcohol or in full-strength formalin, with obvious tissue alterations. The ratio of fixative to specimen size is frequently inadequate, with resulting poor fixation, particularly in central parts. Disposable jars are not used (to reduce costs), being replaced with any type of available container, mostly glass jars, with obvious handling risks. Reagents are imported mainly from low-cost factories, which may not always ensure quality standards. Precise personal and clinical data are often lacking, making clinicopathologic correlations and compilation of databases or registries difficult, if not impossible. This highly deficient referral system has been previously described by Dafaallah et al. (Dafallah et al. 2005).

The maintenance of equipment, especially tissue processors, poses problems, mainly because of unstable power supply, inexperienced maintenance personnel, and difficulty in getting the correct replacement parts. The process from surgical sample to pathologic diagnosis requires several steps to be performed with the aid of instruments that are most often inadequately maintained or out of order.

These problems clearly have deleterious effects on the quality of preparations and on the accuracy of diagnosis. At times, the combined effect of unavoidable and apparently trivial deviations from standard procedures or good practice makes it very difficult to recognize which step should be modified to improve the quality of the microscopic preparations which, in turn impinges on the ability to make an accurate diagnosis. Indeed the lack of ancillary techniques makes it mandatory to have very good microscopic preparations in order to facilitate diagnoses made solely on morphologic grounds. Hence, the limited availability of maintenance services and spare parts for instruments is a major problem. The bulk of the above-mentioned problems are exacerbated by the limited budgets constantly allotted to pathology departments.

These problems cannot be individually addressed. Government investments are needed to support backbone projects for the development of pathology departments. The first step could be consolidation of the existing resources and diagnostic activities in centralized laboratories, which would allow better training and costs optimization. This is the philosophy underlying the establishment of the National Cancer Institute of Sudan at the University of Gezira in Wad Medani.

4.1 The National Cancer Institute (NCI-UG), University of Gezira, Wad Medani, Sudan

The National Cancer Institute, University of Gezira (NCI-UG), is a special center established in 1994 by the University of Gezira (UG) in Wad Medani, Sudan. UG is a community-oriented university established in 1975, with a main objective of rural development. UG is located in the center of Sudan in Gezira state, the most densely populated state, which harbors the Blue Nile-irrigated Gezira Scheme. NCI-UG was established to meet the community's needs in the fields of Oncology, Nuclear Medicine, Medical Imaging and Molecular Biology, integrating activities of research, service and training.

The uniqueness of the approach of NCI-UG in implementing these complementary functions made the institute's environment quite satisfactory in providing medical services,

good quality research, and training programs (Dessein et al. 1999; Mohamed-Ali et al. 1999; Abel et al. 2000; Pascal et al. 2000; Henri et al. 2002; Chevillard et al. 2003; Dessein et al. 2004; Alsheikh et al. 2006; Awadelkarim et al. 2007; Abuidris et al. 2008a; Abuidris et al. 2008b; Abuidris et al. 2008c; Awadelkarim et al. 2008; Dessein et al. 2009; Faggad et al. 2009a; Faggad et al. 2009b; Rahoud et al. 2009; Tofanelli et al. 2009; Awadelkarim et al. 2010a; Awadelkarim et al. 2010b; Elgaili et al. 2010; Elwali et al. 2010; Ali et al. 2011; Awadelkarim et al. 2011).

Its Nuclear Medicine, Oncology, Molecular Biology, Medical Physics and Engineering, Diagnostic Imaging and Medical Laboratories Departments make NCI-UG the only cancer institute outside the capital Khartoum (Figure 9). The growing number of the new cancer patients seen at NCI-UG during 2005-2008 is shown in Tables 3-5. The current status of knowledge on tumor patterns and risk factors in Sudan was comprehensively reviewed by Awadelkarim and co-authors (Awadelkarim et al. 2010a).

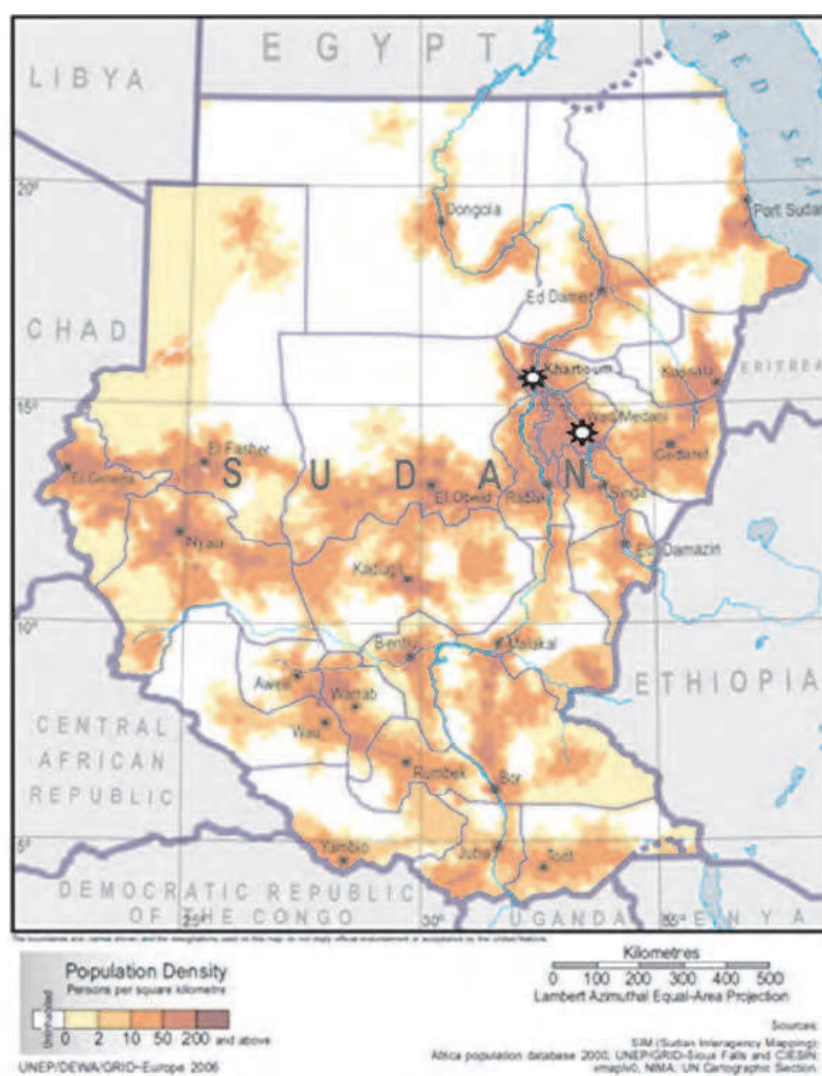


Fig. 9. Distribution of the population in Sudan. The stars indicate the only two cancer institutions, the Radiation and Isotope Center (RICK), and the National Cancer Institute of the University of Gezira (NCI-UG).

Year	Male, n (%)	Female, n (%)	Total, n (%)
2005	270 (44.2)	341 (55.8)	611 (100)
2006	347 (45.1)	423 (54.9)	770 (100)
2007	351 (44.7)	435 (55.3)	786 (100)
2008	416 (46.1)	487 (53.9)	903 (100)
2009	513 (43.8)	659 (56.2)	1172 (100)
Average \pm SD	379 \pm 91	469 \pm 118	848 \pm 209

Table 3. Total number of patients diagnosed with cancer from 2005 to 2009 (Awadelkarim et al. 2010b).

The activities carried out at NCI-UG are mainly related to the diagnosis, management, and prevention of cancer, the use of radioisotopes in medical diagnosis, cancer research, and the training of doctors, scientists and technologists. To successfully achieve these objectives, NCI-UG establishes national and international collaborations with relevant Institutions. Efforts to interact and to solve problems related to pathology services at NCI-UG are ongoing; they include external collaborations with Italy, France, and UK. Currently, bilateral visits with Italian collaborators are regularly taking place.

NCI-UG, with the support of the International Agency for Research on Cancer (IARC), established in 2006 the Gezira Cancer Registry, the first population-based cancer registry in the country. The Gezira Cancer Registry, located at the NCI-UG in Wad Medani, the capital city of Gezira State, covers only Gezira State (Central Sudan, 26,075 km²), serving about four million people (10% of the total Sudanese population). Most recently, in 2009, the Sudanese Federal Ministry of Health also established a population-based cancer registry named "Sudan Cancer Registry" (Awadelkarim et al. 2010a).

The collaboration between NCI-UG and the Curie Institute, Paris, France is supported and financed by the Sudanese Government, the French Embassy in Khartoum, and the *Fondation Pierre-Gilles de Gennes pour la Recherche* in the fields of oncology (i.e. pediatric oncology, breast cancer) and tropical diseases (i.e. schistosomiasis and malaria). The main goals are training and research. Similar activities in pediatric oncology and breast cancer are being conducted in collaboration with the National Cancer Institute, Milan, Italy. Furthermore, cervical cancer screening activities are ongoing in collaboration with the European School of Oncology, Milan, Italy. Notably, the collaboration between the "G. d'Annunzio" University Foundation of Chieti, Italy and NCI-UG is within the framework of activities developed by CeSI as special consultant of ECOSOC of the United Nations. Bilateral exchanges are supported by "G. d'Annunzio" University Funds for Mobility of Researchers and Internationalization outside the European Union and by the NCI-UG.

The lack of precise and timely laboratory-based cancer diagnosis remains a central problem at NCI-UG. As previously mentioned, in Sudan there is no pathology infrastructure which can guarantee the quality of the samples collected, processed and stored, and the clinical or biological data associated. These factors are the main reasons for the poor diagnosis of cancer and the ensuing scarce information on cancer patterns. Thus, as a consequence of the long-lasting scientific partnership between NCI-UG and CeSI Institutions, a specific project to update surgical pathology in Wad Medani was funded by a private foundation, the *CariChieti* Foundation of Chieti, Italy. This intervention integrates traditional educational goals with training periods of young MDs

in the field of diagnostic pathology and the use of telepathology for cases consultation, in order to upgrade the diagnostic capabilities, as requested by the developing and increasing activity of the oncology clinic. Expertise is needed especially for pediatric oncology, and for breast and cervical cancer diagnosis. The partnership for pathology training is based on mutual respect and on the agreement to fully integrate the trained personnel in the pathology infrastructure developed at NCI-UG.

Rank	2005		2006		2007		2008	
	Cancer type	n (%)	Cancer type	n (%)	Cancer type	n (%)	Cancer type	n (%)
1	Prostate	27 (10)	Prostate	53 (15.3)	Prostate	64 (18.2)	Prostate	96 (23.1)
2	NHL	23 (8.5)	NHL	35 (10.1)	NHL	21 (6)	Liver	32 (7.7)
3	Colorectal	19 (7)	Bladder	21 (6.1)	Nasopharynx	17 (4.8)	Nasopharynx	26 (6.3)
4	Nasopharynx	18 (6.7)	Unknown primary	19 (5.5)	CML	17 (4.8)	NHL	26 (6.3)
5	ALL	12 (4.4)	Skin	16 (4.6)	Colorectal	15 (4.3)	Colorectal	20 (4.8)
6	Hodgkin's disease	12 (4.4)	Liver	15 (4.3)	CLL	14 (4)	Esophagus	19 (4.4)
7	Liver	12 (4.4)	ALL	15 (4.3)	Larynx	12 (3.4)	Stomach	14 (3.4)
8	Esophagus	10 (3.7)	Nasopharynx	12 (3.5)	Liver	11 (3.1)	Bladder	13 (3.1)
9	Hypopharynx	9 (3.3)	Esophagus	11 (3.2)	Bladder	11 (3.1)	Lung	13 (3.1)
10	Unknown primary	9 (3.3)	Hodgkin's disease	10 (2.9)	Oral	10 (2.8)	CLL	12 (2.9)
Sub list Total		151 (55.9)	207 (59.7)		192 (54.7)		271 (65.1)	
Total male cancer		270 (100)	347 (100)		351 (100)		416 (100)	

Table 4. The most common ten cancers in males diagnosed at NCI-UG during the period from 2005 to 2008 (Awadelkarim et al. 2010b).

Rank	2005		2006		2007		2008	
	Cancer type	n (%)	Cancer type	n (%)	Cancer type	n (%)	Cancer type	n (%)
1	Breast	105 (30.8)	Breast	163 (38.5)	Breast	147 (32.5)	Breast	195 (40)
2	Cervix	27 (7.9)	Cervix	50 (11.8)	Cervix	38 (8.4)	Ovary	41 (8.4)
3	Ovary	26 (7.6)	Ovary	29 (6.9)	Ovary	31 (6.8)	Cervix	35 (7.2)
4	Esophagus	24 (7)	Esophagus	18 (4.3)	Esophagus	25 (5.5)	Esophagus	28 (5.7)
5	Colorectal	14 (4.1)	Uterus	13 (3.1)	NHL	22 (4.9)	Uterus	26 (5.3)
6	NHL	10 (2.9)	NHL	12 (2.8)	Uterus	13 (2.9)	Colorectal	17 (3.5)
7	CML	10 (2.9)	Unknown primary	11 (2.6)	Colorectal	12 (2.6)	Bladder	15 (3.1)
8	Hypopharynx	9 (2.6)	AML	9 (2.1)	Hypopharynx	12 (2.6)	AML	14 (2.9)
9	Nasopharynx	9 (2.6)	CML	8 (1.9)	Nasopharynx	11 (2.4)	CML	13 (2.7)
10	Liver	9 (2.6)	Nasopharynx	7 (1.7)	Liver	10 (2.2)	Unknown primary	11 (2.3)
Sub list Total		243 (71.3)	320 (75.7)		321 (70.9)		395 (81.1)	
Total female cancers		341 (100)	423 (100)		435 (100)		487 (100)	

Abbreviations: ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia.

Table 5. The most common ten cancers in females diagnosed at NCI-UG during the period from 2005 to 2008 (Awadelkarim et al. 2010b).

5. New technologies for North-South collaboration: Telepathology

The advent of digital photography opened a new era in diagnostic pathology allowing easy sharing of single microscopic photographic images, and this resulted in the rapid development of “static” telepathology (Figure 10) (Guzman & Judkins 2009). In the mid 1990s scanners capable of scanning whole microscopic slides were introduced, and dynamic high resolution images by first generation slide scanners became available around 2000. This prompted the development of “dynamic telepathology”: in fact, with whole slide imaging (WSI) the restraints of “static telepathology” were overcome and transfer of diagnostic capability became a reality (Figure 11).



Fig. 10. The basic instrumentation for static telepathology is simple and inexpensive: a trinocular microscope coupled with a digital camera and a web connection.

This new technology may help in dealing with the dramatic shortage of pathologists and trained technicians in sub-Saharan Africa in front of the forecasted increase of incidence of cancer in Africa. The *Associazione Patologi oltre Frontiera* (APOF) developed pilot projects in Zambia and Madagascar to test “on the field” the impact of the new technological developments, utilizing both static and dynamic telepathology. Depending on local conditions, teleconsultation and distant quality assessment of local diagnostic activity are used where the number of local pathologists is adequate, while distant diagnosis is necessary where local pathologists are scarce or absent. Based on field experience, the following steps are essential:

1. Careful choice of hospitals with high-speed internet connections, especially in upload (ADSL or optical fibers are suitable for WSI). Peripheral hospitals far from cities are generally unsuitable, as they would need a satellite link, too expensive for a single small center.
2. Local availability of at least two laboratory-certified technicians (even personnel with high school degree or nurse formation may be involved).

3. Training of local technicians to Pap test evaluation. After about six months of intensive teaching, technicians are generally able to prepare and stain standard cytological preparations, such as Pap smears. Similar training of local technicians can be done for histological techniques (fixation, embedding, cutting, staining and mounting histological slides). Training generally requires the on-site presence of expert technicians that supervise availability and correct use of the instrumentation and reagents.

When slides are ready they are scanned (WSI) and transferred to the server. The on duty telepathologist studies the case and signs out the diagnosis. Gross sampling can be performed by technicians (if no pathologist is locally present) with online supervision, pending availability of adequate macro-connections. Macroscopical description, microscopical evaluation and final diagnosis are loaded in the program with other available patient data and the final report is signed out.



Fig. 11. For dynamic telepathology a slide scanner and a fast web connection with a server are mandatory. Costs are high but diagnostic and educational potentials are huge.

6. Conclusion: Searching versus planning

Passive participation in programs originating abroad generally does not work. Presently there is no consensus on how to help developing countries, and it is debated whether large centrally coordinated efforts are needed, or more simple solutions guided by innovative people “on the ground” (Easterly 2006; Benediktsson et al. 2007). This debate is complex, and should be familiar to pathologists who would like to get professionally involved in health care in developing countries or who simply want to understand the problems (Benediktsson et al. 2007; Hassan 2007b). However, the two diverse approaches are complementary, rather than alternative.

It has been pointed out that huge amounts of money were spent by international agencies in ambitious and elaborated development plans that had limited results. To counteract this risk, it is necessary to have a continuous feed-back of the results obtained, and the flexibility and ability necessary to find new approaches and establish new goals, that might be quite different from those originally planned (Easterly 2006). A practical approach, with direct involvement of the local population and attention to suggestions coming from local experts acting with open mind and creativity, is always necessary (Easterly 2006). Actually the

original "searchers" are the local inhabitants, and some of their original approaches could be endorsed by actors coming from abroad (Easterly 2006). Thus, the identification of local partners with accountability is crucial for every project of intervention in pathology, as such partners could provide not only help, but also innovative solutions on their own.

Clearly, a volunteer approach from abroad cannot meet the need for diagnostic capability in sub-Saharan Africa. The development and strengthening of local skills remains crucial for improving local diagnostic performances.

Indeed, the development of pathology in sub-Saharan Africa reflects the complex spectrum of the educational, cultural, political and economic challenges that must be addressed to build basic biomedical capabilities in the developing world (Gray & Carter 1997; Hassan 2007a). In this regard, the pathologists, academic institutions, and health centers from the developed countries of the North are called to provide help.

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To better understand the contemporary world, the world of innovation and technology, science should try to synthesize and assimilate social science in the development of our civilization. Does the new era require new knowledge? Does the age of globalization demand new education, new human attitudes? This book tries to clarify these questions. The book *New Knowledge in a New Era of Globalization* consists of 16 chapters divided into three sections: Globalization and Education; Globalization and Human Being; Globalization and Space. The Authors of respective chapters represent a great diversity of disciplines and methodological approaches as well as a variety of academic culture. This book is a valuable contribution and it will certainly be appreciated by a global community of scholars.

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