A HISTORICAL REVIEW OF PAST HISTOPATHOLOGICAL MATERIAL AT THE SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH BETWEEN 1911 AND 1927*

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The late Dr. F. W. Simson used to say that after a bacteriologist made his diagnosis, he could throw away the slides and cultures; the histopathologist's slides on the other hand were filed and his diagnoses were always open to review. This may encourage the histopathologist to deliberate before committing himself, and has the great advantage that, with progress in the recognition of disease, later investigators may review old material with newer criteria and techniques.

Kaposi's Sarcoma

The present study is an example of this, the problem arising as a result of the long-standing interest of Prof. J. F. Murray in Kaposi's sarcoma, a condition that is relatively common among the Bantu, although exceedingly rare among the White, Coloured and Asian races. Kaminer and Murray[1] found that this disease had not been diagnosed at this Institute before 1942 and the question has naturally been asked whether it is of recent development among the Bantu or had simply been missed in the past. Since the histopathological slides are available from 1911 (shortly after the founding of this Institute), it is possible to find an answer to this question.

I have therefore gone through the records from 1911 to 1927 inclusive, selecting for microscopic examination all tumours of the skin in the Bantu or in persons of unstated race, as well as other possible relevant lesions. As expected, cases were found which histopathologically are typical Kaposi's sarcoma — in fact, the first two Bantu skin cancers were of this type. Clearly, the apparent absence of this disease was due to failure to recognize it.[2]

Increase in Histopathology

The survey of these old records, however, uncovered much more of historical and histopathological interest, and has some bearing on present policies.

An extraordinary increase is apparent in the use of histopathological confirmation. For the first 4 years the annual number of specimens amounted to between 200 and 300, but thereafter it increased in something close to geometric progression — 390 in 1918, 819 in 1922, and 1,446 in 1926. The figure rose to 4,000 in 1940, 9,000 in 1948, and by 1953 had reached 20,000 *per annum*. The formation of branch and private laboratories has enabled segments of this material to be taken over, but the rate of expansion has consistently outstripped expectation as well as staff. Planners, if such existed, failed to interpret their information. This probably explains why more use has not been made of this mine of research material.

Records

Illegibility of records was a problem then as now. Good handwriting, which should be a primary qualification for the keepers of record books, appears to have been fortuitous and to have had nothing to do with the appointment of the recorder. Permanent records demand legible and attractive script, and the casual wielder of the hasty ball-point pen has no place here. Having recently read 11,000 entries, I make this point with some feeling.

The records were often defective, and frequently failed to state the patient's name, age or race. Some bore no identification other than the sender's name, presumably because the submission of a specimen for biopsy was so rare that confusion was improbable. Other specimens identified the patients as 'A. B. C.', 'X. Y. Z.', 'old man', 'an elderly lady', 'pauper' or 'bed 57'. The records would have had greater value today had complete information been insisted on. Clinicians still fail to appreciate the importance of such information. Meticulous care is justifiable, for records become the material with which the history of pathology and public health can one day be written — a history which furthermore is not dependent solely on the diagnostic acumen or the state of knowledge at the time when the work was originally carried out.

Much more interest was shown in the nationality of the individual than at present. The familiar labels, 'European' and 'Native' occurred, but many were described more precisely, e.g. Jewish, Dutch, British, Danish. The term 'Kaffir' was very rarely employed, 'African' being the commonest designation for the Bantu races. (This may be of interest to those who consider this a recent expression of African nationalism.) Many of the records also stated the skin, hair and eye colour of the patient.

This interest in origin may well have arisen as a result of Dr. Watkins-Pitchford's[3] theory that skin pigmentation had something to do with susceptibility to cancer. He had noted the liability of the albino Bantu to skin cancer, and drew the natural conclusion that sunlight was carcinogenic. He carried this further, however, believing that exposure to sunlight might explain almost all the racial differences in cancer he observed. The flights of fancy that this resulted in make comical reading from the present vantage point. The higher breast-cancer susceptibility of Whites was attributed to *décolleté* garments, and uterine and prostatic cancers to the effect of a full bladder, acting as a lens, focusing the carcinogenic rays deep in the pelvis. The relative immunity of the clergy to cancer was attributed to the clerical garb. Similarly, male stomach cancer was related to the habit of removing the waistcoat and the lenslike action of the beer-filled stomach. A piece of photographic paper might have told him that these rays do not get below the skin, but those were the days of untested speculations. At least the racial differences had been recognized and an explanation attempted.

Among the Bantu there was the usual variety of frivolous names, introduced perhaps by the miners with whom they worked, faced with the original problem of Mr. Bumble in *Oliver Twist* of naming a large number of undistinguished and relatively indistinguishable individuals. To the same flippancy, presumably, we may ascribe such names, or nicknames, as Lice (a favourite one, this), Watch, Kipper, Cyanide, Notch, Flower, Matches, Sokkies, Canteen, Porridge, House, Bye-Bye, Nickies, Fifteen, Satin, Long One, Basket or Tickey. Such designations have long disappeared from the records.

Diseases in the Bantu

The early material was stained with haematoxylin-van Gieson, the acid fuchsin of which has long since faded. Haematoxylin and eosin was introduced a few years later, but even so, duplicate sections stained with the old method were included.

Even a superficial observer could not fail to note the differences between the disease pattern in the Bantu of those days as compared with the present. In retrospect the number of specimens of syphilitic and tuberculous disease is terrifying. Tuberculomas outnumbered by far all other tumours of the brain. Tuberculosis was the commonest lesion of the testis. The picture is one of rampant disease in a highly susceptible population.

Syphilitic lesions were extraordinarily common in their distribution and number. Gummas of all sites, especially of brain, heart, liver and testis, were encountered. Today, gummas are exceedingly rare. In those days they came second to tuberculomas. Cases of leprosy abounded, as did typhoid, amoebiasis, and fatal blackwater fever. One can speculate what the effects would have been had the introduction of antibiotics and specific therapy been delayed a few more decades.

A multitude of specimens of pneumonia in the stages of red and grey hepatization are available and serve as another reminder of what we owe to antibiotics. These pathological specimens will become increasingly rare as antibiotics are

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universally employed and the demonstration of the various stages of the untreated disease will become more and more difficult at medical schools.

Maduramycosis seems to have been commoner than at present and, significantly, one case (9,105) came from Graaff-Reinet. This demonstration of a disease typical of forested areas from an area now devoid of afforestation is a testimony to the profound changes that have been occurring in the vegetation of this country with the spread of agriculture, soil erosion and the desert.

Animal Parasitic Diseases

Animal parasitic diseases were very common. Bilharziasis appeared in many sites, and Pirie[4] observed the association between bilharziasis and primary carcinoma of the liver, and at first believed this was causal. He later admitted the possibility of other causes when cases were found of the cancer without the parasite;[5] the combination is probably a coincidence arising out of the frequency of both diseases in Moçambique mine labourers.

An interesting specimen (4,262) is a malignant adenoma of the liver in a Chinese, associated with *Clonorchis sinensis*. This proved to be a hepatocellular carcinoma, and not the bile-duct carcinoma so typical of infestation with this parasite.[6] Had it been a bile-duct carcinoma it would have stood out in even greater contrast against the background of the experience at that time of primary carcinomas of the liver in the Bantu, which, as Pirie had shown,[4] were by far the commonest tumours in the Bantu. Many of the primary carcinomas of the liver were diagnosed as of bile-duct origin — most of these on re-examination prove to be adenoid hepatocellular tumours.

Cysticercosis of the brain was frequently described, including one case (2,575) diagnosed as *C. bovis*. This was based on a section through the scolex, but unfortunately the section does not pass through the rostellum, so it is not possible to be sure that hooklets are absent. This diagnosis must therefore be regarded as not proved.

Another specimen (1,223) is of larvae diagnosed as *Calliphora vomitoria* passed per rectum by a child of 3 years. Dr. F. Zumpt's comment on this is that *Calliphora vomitoria* does not occur in South Africa and in any case it is impossible to identify the species of a first instar *Calliphora* larva. The specimens are first instar *Sarcophaga* larvae, most probably *Sarcophaga haemorrhoidalis* (Fallen). Dr. Zumpt regards it as almost certain that these larvae were deposited in the stool after it had been voided, the only other possibility being that the fly, which is viviparous, deposited the larvae on the contaminated anus. The records state that a dose of 'santonin' resulted in many more being found, but this does not convince the modern sceptic.

Nomenclature of Tumours

There is some interesting evidence of development in pathological nomenclature. The mixed tumours or pleomorphic adenomas of salivary-gland origin, for example, appeared in the earlier years as teratomas. The diagnosis changed within a year or two to endothelioma, sometimes sarcoma and myxoepithelioma, before eventually appearing as compound parotid tumour, mixed-cell tumour, and mixed tumour of the salivary glands.

Just as salivary tumours gave difficulty in recognition, so did adnexal tumours of the skin, so that hidradenoma appeared in consequence as a malignant adenoma (1,492) or as 'lymphangioma' (2,808). (The term lymphangioma was employed much more freely than it is today, as also was the term 'endothelioma', which applied to many spindle-cell tumours, including, as mentioned above, the mixed tumours of salivary glands.) 'Epithelioma' was synonymous with squamous-cell carcinoma, and pseudoepitheliomatous hyperplasia, it appears, was not always distinguished from true carcinoma.

The pathological classification of sarcomas tended to be simple. Large and small round-celled, and large and small spindle-celled sarcomas comprised the bulk of these lesions. Occasionally myxosarcoma and angiosarcoma were distinguished, but rhabdomyosarcoma with clear cross-striations passed unrecognized. On the other hand melanomas were separated into melanotic carcinomas and sarcomas. Despite a broad acquaintance with the infectious lesions, some granulomas were diagnosed as sarcomas, and the term 'sarcoma' in general had wider boundaries than it enjoys today. It also included, besides salivary-gland tumours, the oat-cell carcinomas of the lung. In consequence, and also because of the age distribution of the population, the sarcoma: carcinoma ratio among the Bantu appeared unduly elevated in many early studies like that of des Ligneris.[7]

On the credit balance was the recognition that the spindle-cell sarcomas of the abdominal wall might be locally malignant only. The diagnosis of soft-tissue tumours is still defective, and later workers in histopathology will probably find most to correct in this region of subtle morphological and biochemical cellular differences.

Carcinoma of the Lung

Carcinoma of the lung in Whites was relatively rare, partly because some were classified with the sarcomas, but evidently the incidence was low, and in the 1927 Annual Report[8] there is special mention of 'the occurrence of two of the relatively rare primary carcinomata of the lungs in the European group' (of postmortem examinations). Many authors (e.g. Willis[9]) have explained the low figures for cancer of the lung in the past on the grounds of misdiagnosis. Misdiagnoses certainly occurred, but cannot entirely account for the impression current in 1927, or in 1903 when Bland-Sutton[10] wrote:

> 'The immunity of the mucous membrane of the nasal passages, the naso-pharynx, the trachea, bronchi, and lungs from primary cancer is remarkable; with the exception of the heart, there is no organ in the body which is so rarely occupied by a primary malignant tumour as the lung. In the few cases recorded as primary cancer of the lung there are good grounds for the belief that the disease arose in the mucous glands of the bronchi.'

It is difficult to believe that any pathologist, however much in error, could write this today, and Bland-Sutton's concluding sentence suggests a relative preponderance of Kreyberg's Type 2 (the adenocarcinomas), as one might expect if the increase were recent and confined to Type 1.

Miscellaneous

Quack therapy of cancer was encountered, of course. A specimen (962) of breast treated with a cancer plaster reveals no tumour, but an area of necrosis and leucocytic infiltration is present; the leucocytic infiltration is less heavy than one usually encounters in such material. Many of the characteristic African diseases were then well known, and ainhum, onyalai and keloids appear repeatedly.

There is a sprinkling of pathological rarities, for example the postmortem findings of a case (2,558) of amaurotic family idiocy, showing the classical features. Lipid stains are not available, and the case would have been many times more useful if the wet specimens had been preserved. The impossibility of keeping all material is too often made an excuse for not keeping any. Anyway, even if the wet specimens cannot be retained, there is always the possibility of taking multiple blocks for future generations to examine.

In 1926 there appeared (9,616) the first specimen diagnosed as haemochromatosis by Dr. A. S. Strachan, who had come to the Institute in 1923. It is a typical example of haemosiderosis of the hepatic parenchyma with minimal portal fibrosis. A hepatocellular hepatoma is present and, significantly, the pancreas shows no haemosiderin deposition. This first case should have suggested that the Bantu haemosiderosis was not the same disease as haemochromatosis. Although the possibility of excessive iron intake was mooted, it took another 27 years before Walker and Arvidsson[11] published the iron-overload hypothesis, and the story is not yet complete.

A few extraordinary diagnostic excursions are encountered — one such (5,149), for example, was a diagnosis of ectopia testis from the postanal margin. The section shows a leiomyoma accompanied by tubules, admittedly not unlike epididymis, but possibly derived from the anal ducts, perhaps from a small sacrococcygeal teratoma.

Another interesting specimen (5,718) is a piece of the upper

lip of an African from Cathcart, diagnosed as '? early carcinoma. Necrosis of muscle' on 8 November 1923. Histologically this is a classical granular-cell myoblastoma, with pseudoepitheliomatous hyperplasia — a condition which Abrikossoff[12] was to describe 3 years later.

Kaposi's sarcoma, as indicated, was not recognized and appeared as spindle-cell sarcoma, malignant melanoma, and once even (in 1926) as angiosarcoma. Lack of contact by the pathologists with the clinical aspects of their cases was probably to blame. We aim to recognize clinicopathological entities, and pathology carried out in isolation, although able to distinguish the well-known or clear-cut diseases, must remain second-rate when it comes to the unusual.

Not a single specimen of oesophageal cancer from an African was noted in the entire series of histological specimens, in which over 100 cases of cancer of the liver were reported, for primary carcinoma of the liver in the Bantu formed between 1 and 2% of all specimens from all races. Two postmortem examinations on Africans with primary carcinoma of the oesophagus are mentioned in annual reports, in 1926[13] and 1927,[8] but histological confirmation was not considered necessary in necropsy investigations in those days. Strachan[14] found 3 cases between 1924 and 1935, during which period there were 37 primary carcinomas of the liver. When one bears in mind that in some hospitals at present carcinoma of the oesophagus is commoner than carcinoma of the liver among the Bantu, it will be appreciated what a tremendous change has taken place — a change so great that it cannot simply be explained by diagnostic techniques.

Hodgkin's disease was often diagnosed in Bantu cases, so that the opinion current among some clinicians that Hodgkin's disease does not occur in the Bantu, cannot be blamed on the histopathologists.

The diagnosis of a carotid-gland tumour (8,017) in 1925 was a *tour de force* and it is probable that the pathologists of those days would show up the modern workers in their ability to pick up the commonplaces of the early days that now have become rarities.

Animal Material

Just as the Colonial Bacteriological Laboratory, which was set up in 1892 in Grahamstown for the investigation of animal diseases, cooperated in the early investigations into human cancer,[15] so the South African Institute for Medical Research in Johannesburg also served to investigate animal specimens.

Specimen 319 showed sections of rabbit's ear which had been treated by Dr. H. Bayon on Robben Island with aqueous extracts of gas tar. These specimens from 1912 did not reveal indubitable carcinoma, but then Bayon[16] had gone astray in 3 respects — he injected instead of painting the surface, he used an aqueous rather than an ethereal extract, and finally he killed his animals after a month. In this way, although he antedated the work of Yamagiwa and Ichikawa[17] by 3 years, Bayon failed, as others had before him, to produce cancer. It is said that the Japanese succeeded where others failed because they wrote with a brush, and so the idea of painting as a mode of application came naturally to mind. In such apparently trivial respects, a research worker may make or miss the discovery of a lifetime.

Among the animal material is also to be found the liver of a springbok with focal necrosis (360), a sarcoma from the occipital region (379) and the testis (6,527) of a fowl, and an elephant heart (2,843) from which an agonal clot was submitted.

One wonders what lay behind these specimens. Most of these were probably examples of random curiosity, e.g. the specimen (116) of mature spermatozoa from a dog, but some showed more serious thought — such as the lungs of a horse which had spent 12 years underground (they revealed no sign of silicosis).

Preservation of Specimens

It is tragic that the blocks of this treasury of rare and interesting conditions are not available. During World War II, because of a shortage of paraffin wax, the blocks were melted down and this irreplaceable material was thrown away in a moment of thoughtless and arbitrary expediency. This move was arrested when discovered by Professor Murray, but not before all blocks earlier than 1929 had been lost. It seems hard to believe that paraffin wax could have been so difficult to come by — that candles could not have been used instead. A glance at a chart of the number of specimens received would have shown that two decades of the early period would not have provided enough wax for a single year in the 1940's. In view of the historic value of the material so wantonly destroyed, such a blunder serves to emphasize the importance of the preservation of present material.

The pioneer work done by des Ligneris met an even worse fate — his slides as well as his blocks have disappeared. Without such records it is impossible to check his claims critically, apart from his publications. By contrast, in 1959, in collaboration with Dr. J. Clemmesen, I was privileged to go over the original preparations of Fibiger in Copenhagen, and re-examine his claims to have produced cancer in rat stomachs by infection with the parasite *Spiroptera*.[18] From these, and from his sections of so-called metastases, we could conclude with confidence that he had not produced cancer. The gastric lesions were pseudoepitheliomatous hyperplasia; the lymph-nodal 'metastases' were examples of squamous metaplasia in epithelial inclusions; and the lung 'metastases' were squamous metaplastic lesions in bronchi, subjected to vitamin-A deficiency and bronchiectasis. By comparison, a judgement on published photomicrographs alone is much more difficult and arbitrary and far less convincing. (In discounting Fibiger's claims, which earned him the Nobel prize, one should acknowledge that they exercised a profound significance historically, for they provided the direct stimulus for prolongation of the Japanese research that led to the discovery of the carcinogenic activity of the aromatic hydrocarbons.) In Fibiger's case the material was preserved owing to the devotion of his secretary.

The need to preserve blocks of tissue has not yet been appreciated, it would seem, for I learn that much of the material collected at Baragwanath Hospital has been lost through inadequate storage. From the short-term point of view, the diagnoses have been made, and the loss is immaterial from the restricted viewpoint of Provincial Hospital services, which still hold that their main duty is treatment — as though treatment were something that arose like Pallas Athene in full panoply from the brain of Zeus.

Preservation of wet specimens is another problem, imposing far greater demands on storage space and protection of specimens than does preservation of blocks. This will probably never be kept up, but much can be said in favour of keeping specimens of all rare and little-understood conditions, and perhaps all specimens of 1 year in 20. Just as we have an International Geophysical Year, so we need an 'International Histopathological Year', during which material that is representative of diseases in each country will be preserved for future study or comparison. The commonplace of any region at a given time are often the rarities of other times and places. We easily underrate local experience.

Imagination, Research and Finance

Looking back over these years thus provides a mirror of current weaknesses. Individual imagination and effort there was in plenty, but the determination to finish what looked promising, the recognition of fields that needed to be exploited with all their resources, taking the problem far beyond the boundaries of an individual worker's imagination, seems to have been lacking. If the truth be told, the authorities were not in earnest about medical research. If they had been, would Bayon's experiments have petered out ignominiously, along with so many other promising lines? The first iron lung in the world was made at this Institute in 1918 by Steuart.[19] Some of the first clinical cases to be treated with local applications of crude penicillin were on the Witwatersrand and the antibiotic was made at this Institute. The report for 1930[20] reads:

> 'By the courtesy of Dr. A. Fleming, of St. Mary's Hospital, in London, cultures of a species of penicillium which he had found to possess an inhibitory action on the growth

of the more commonly occurring Gram-positive organisms were used in experimental work. Dr. Fleming's findings were confirmed . . . On the part containing penicillin, colonies of Staphylococcus, Streptococcus, and other Gram-positive organisms did not appear, with the result that the colonies of *B. influenzae* could more easily be detected and picked off . . . Penicillin agar was found to be useful, too, in the easy isolation of *B. pestis* from mixtures of this organism with Gram-positive bacteria.

'The treatment of various infections due to Gram-positive organisms by means of penicillin was tried in a few cases with some success. This work is being continued. An attempt is being made to obtain a more potent extract of the fungus by growing it in a more suitable medium.'

It is easy to criticize from the post-Florey position, after new techniques, like paper chromatography, and the vast financial and technical resources of modern pharmaceutical firms have been put to work on the problem. Nevertheless, someone blundered in 1930 or 1931. In 1929 Sir Spencer Lister wrote of the Institute for Medical Research:[21] 'It is not too much to hope that by its means the Union of South Africa may vie with older established countries in adding materially to the sum of human knowledge of the diseases that affect mankind'. That it has done this is undeniable, but given more money, much more could have been done. An annual grant for research 'not exceeding £5,000' from the Witwatersrand Native Labour Association, and £5,000 from the Government[22] does not suggest a burning zeal for material additions to the sum of human knowledge. (Not surprisingly the sum allocated proved inadequate by the following year.)

Despite the foregoing criticisms there are in these early days notable evidences of this broader imagination. There is the research fellowship awarded to Dr. M. J. A. des Ligneris, a surgeon trained under Kocher, who had carried out original studies in cancer demography while at Elim Hospital. This maintained a cancer research worker who later gained international recognition, at a time when authorities in the country were openly opposed to the idea of South Africa subsidizing cancer research. Perhaps even more impressive, though less substantial, was the granting of an honorarium of 100 guineas to Dr. Adrianus Pijper, a general medical practitioner residing at Bethal, in consideration of his work on diffraction micrometry. 'That original work of high quality should have been accomplished in such unfavourable circumstances, and at his own expense, reflected, in the opinion of the Board, great credit upon Dr. Pijper, and should prove an encouragement to other practitioners similarly situated.'[23]

The germ of a Medical Research Council was undoubtedly present. What was lacking was the money to make it effective.

Conclusions

The golden jubilee of the Institute is already upon us. It is to be hoped that this will further historical accounts of the past 50 years. History, and especially medical history, is not merely of sentimental or patriotic interest, but has a direct bearing on the understanding of diseases, and on theories of their causation. In the meanwhile adequate preservation of material, especially in the transition period from primitive to Western manner of life, is our responsibility. Such material will be invaluable to our successors; 'her children arise and call her blessed' is the reward of the virtuous woman in the Book of Proverbs. With careful records and adequate stores of tissue, our intellectual descendants may one day reward us in the same manner.

SUMMARY

1. A review of the histopathological material in the South African Institute for Medical Research between 1911 and 1927 emphasizes the extraordinary change in disease pattern which has already taken place in the South African Bantu.

2. There is a need for legible and detailed record-keeping, and for preservation of slides, blocks and sometimes tissues.

3. It is suggested that every 20 years an International Histopathological Year is desirable, during which meticulous record-keeping, together with preservation of specimens, will be undertaken by strategically placed institutions. This will facilitate retrospective research.

4. A few poignant examples of missed opportunities in medical research are quoted to disturb any incipient complacency in higher circles.

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