PRIMARY CARCINOMA OF THE LIVER IN INFANCY: WITH A CASE REPORT OF A COLOURED INFANT

RONALD P. BENSON, M.B., CH.B. (CAPE TOWN), M.R.C.P.E., D.C.H.

Late Senior Registrar, Department of Paediatrics of the University of Stellenbosch, and the Karl Bremer Hospital, Bellville, Cape

Primary carcinoma of the liver in infants of all races is rare.[5,26,35] In Southern Africa primary carcinoma of the liver is a common tumour among adult Bantus.[4,12,20] In a recent survey in Natal, Wainwright and Roach[31] found that it accounted for 30% of all primary alimentary carcinomas among Bantus, as compared to 2% among Europeans and Indians. In all but exceptional cases among the Bantu, the tumour is associated with cirrhosis, either nodular hyperplasia or diffuse hepatic fibrosis with or without siderosis.

On the other hand, it is most unusual to find cirrhosis in infants and children dying of primary liver carcinoma.[28] Despite the close histological resemblance of liver carcinoma in the infant and the adult, no common aetiological association appears to be present. The condition has been described in a newborn infant, and in the first week of life.[36,37] The occurrence of the tumour at such a very young age suggests that, like the Wilm's tumour of the kidney, it may have its origins *in utero*. Some unusual stimulus to neoplasia or developmental dysplasia seems to be present when liver cells become malignant in infancy.

No case of primary carcinoma of the liver occurring below the age of 1 year has been recorded in Southern Africa. The youngest case observed in the Bantu is a child of 10 years,[19] although a male Bantu child of 7 years is mentioned.[31]

CASE REPORT

A 4-months-old Coloured male infant, J.L., was referred by Dr. O. D. Mollett of Merweville, Cape Province, for investigation of an abdominal mass. He was a full-term infant, but the birth weight was not recorded. He was entirely breast-fed and the 5th child in the family, the other children being alive and well. Six weeks before admission the mother noticed a lump in the abdomen, which had increased appreciably in size. The infant had become somewhat lethargic and had lost weight. No disturbances in bowel function, nor any urinary complaints had been noted. No family history of cancer could be obtained, nor was there exposure on the part of the mother or father to radiation before or during the gestational period.

Examination on 15 August 1957 revealed a contented-looking infant weighing 13 lb. 12 oz. There was evidence of recent weight loss. Temperature was 100°F rectally. The *abdomen* was distorted by a very large, hard, somewhat irregular and nodular mass extending below the costal margins on both sides. On the right side it filled the entire lumbar space and stretched 2 fingerbreadths below the umbilicus across the mid-line to the left renal angle. The mass moved slightly with respirations and it was not obviously tender. No free fluid in the abdomen was detected. The spleen was not palpable and the genitalia were normal. No clinical anaemia, jaundice or dyspnoea was noted, and there were no skin rashes or purpura. The rest of the examination was normal.

The provisional diagnosis was made of a right-sided Wilm's tumour (renal embryoma).

Investigations showed: Hb 9·4 g.% (normal 10·5-12·5 g.%), white cells 19,800 per c.mm., lymphocytes 55%, polymorphs 40%, monocytes 5%; blood Wassermann reaction negative. Serum proteins: albumin 4·9 g.%, globulin 2·0 g.%, total 6·9 g.%.

Serum bilirubin 1·9 mg.% (normal 0·1-0·8 mg.%). Serum cholesterol 245 mg.% (normal 100-200 mg.%). Blood urea 23 mg.%.

Liver function tests: Thymol turbidity 3·5 units, thymol flocculation 1 unit, zinc sulphate turbidity 4 units.

Straight X-ray of the abdomen showed a soft-tissue mass, occupying the whole of the upper abdomen and extending to the brim of the pelvis and displacing the intestines downwards. The gas shadow of the hepatic flexure of the colon was not seen. No areas of intra-abdominal calcification were visible.

X-ray of the chest showed increased lung markings at the right lung base, whilst the right leaf of the diaphragm was raised and indefinite in outline.

Intravenous pyelogram (using 5·5 ml. of 76% urografin) showed good function of both kidneys. The calyceal pattern of the left kidney was normal. The right kidney was displaced downwards

and showed slight distortion of the middle and lower calyces, which filled poorly.

Progress. The infant's condition steadily deteriorated with elevation of the temperature, pulse and respirations and he died on the 4th day after admission.

Autopsy was carried out some 34 hours after death.

The body was that of a fairly well nourished Coloured male infant. On opening the abdomen a cupful of clear straw-coloured fluid was present in the abdominal cavity. No peritoneal nodules were seen. A very large liver tumour was found to occupy the entire right side of the abdominal cavity. The liver mass was adherent to the diaphragm above and to the right kidney, which it had displaced downwards, but it did not appear to be infiltrating these organs. The tumour was uniformly firm and nodular. The liver weighed 855 g. Cut section of the liver showed that the

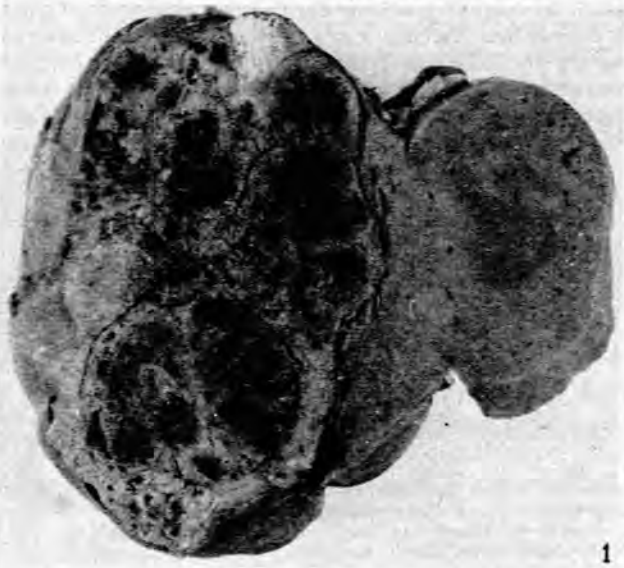

Fig. 1.

entire right lobe was occupied by a tumour which was well demarcated from normal liver tissue of the left lobe (Fig. 1). The tumour appeared to arise from one focus. It was fleshy in colour with scattered areas of haemorrhage but no obvious necrosis. Running through it were strands having the appearance of dense fibrous tissue, which gave it an over-all lobulated appearance. The hepatic and portal vessels were free from thrombus formation.

The heart, kidneys, brain, spleen, lungs, adrenals and testicles appeared normal.

Histology. Liver (Figs. 2 and 3). Dr. T. Mulligan reported: 'The tumour mass is formed by large polyhedral cells, resembling normal parenchymal cells. There is a tendency in certain parts of these cells to form lobules with sinusoids and a central vein. There are also areas of necrosis and haemorrhage. A few fibrous septa are present and appear to contain structures resembling bile ducts. The surrounding liver tissue shows atrophy and fibrosis. The left lobe appears normal with no evidence of fibrosis. The appearances are that of a well differentiated liver-cell carcinoma (malignant hepatoma).

The *spleen* is congested and shows prominent reactive follicles. The *lungs* show congestive changes and oedema with a few inflamatory cells. No histological evidence of metastases is present in these organs, nor in the heart, kidneys, adrenals or brain.'

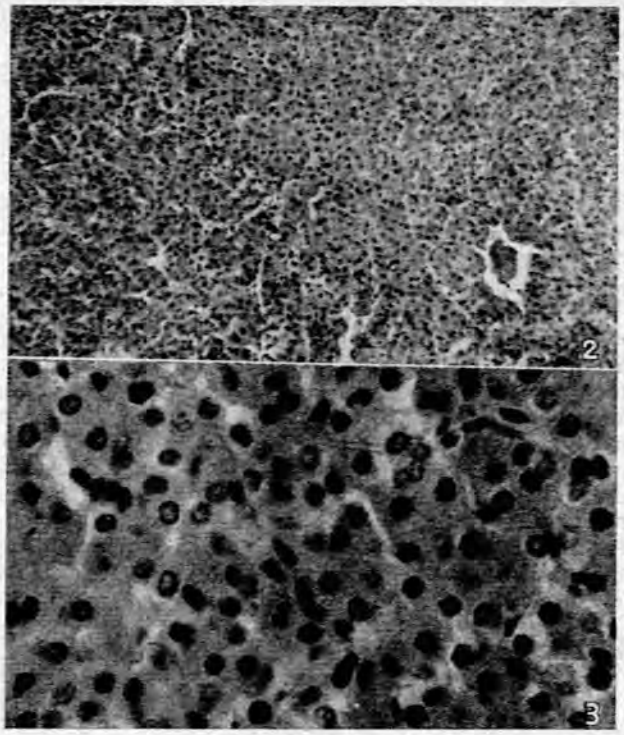

Fig. 2 Low power.
Fig. 3. High power.

ASPECTS OF THE DISEASE

Pathology

Primary carcinoma of the liver may be derived from the cells of either the liver parenchyma or the bile ducts, that is, malignant hepatoma and malignant cholangioma. In some instances, a mixture of these two may be found in different parts of the same tumour, in which case the cholangiocellular variety usually predominates over the hepatocellular.

The subject of primary carcinoma of the liver in infancy and children has recently been reviewed by Bigelow and Wright.[5] The authors discuss some of the difficulties in deciding which cases in the literature were true malignant diseases of the liver, in order to exclude benign tumours such as adenomas and hamartomas, and malignant growths such as haemangio-endotheliomas. In all they collected 95 acceptable cases, including one of their own. By far the commonest type was the liver-cell carcinoma (60), 3 were of the bile-duct type, and the others were reported as mixed. Few were associated with cirrhosis.

The gross types have been described as massive (lobar), nodular or diffuse. When nodular the tumour is believed to represent a widespread intrahepatic dissemination. Extrahepatic metastases are noted in about one-third of the reported cases.

Malignant liver cells tend to resemble normal parenchymal cells, but a considerable range of cytological structure may be found. Some parts of a section may show variations from well to poorly differentiated types. The well differentiated cells are cuboidal and discrete, and have a definite but faint cell membrane, and a faintly granular and abundant cytoplasm. These cells are arranged in cord-like manner and may be found projecting into vascular spaces. Mitotic figures are usually scanty. Cells are frequently found invading normal liver tissue, or extending into hepatic veins or through the liver capsule. There is usually a complete lack of lobular formation of normal liver tissue. Portal or hepatic veins may contain tumour thrombus. Spontaneous non-neoplastic portal-vein thrombosis is an important

complication seen in adults but not in infants. Dense stroma composed of collagen strands are frequently found dividing the tumour when it is unicentric in origin. Areas of haemorrhage and necrosis are commonly seen.

Several malignant liver tumours in childhood appear to be of a mixed embryonal or teratoid origin.[14] They are sometimes referred to as embryomas. The histological pictures of these tumours are extremely varied and include tissues from all parts of the body, commonly osteoid tissue. Depending on what tissue predominates, they are reported in the literature as malignant liver-cell carcinoma, embryonal hepatocellular trabecular carcinoma, or occasionally as 'unclassified carcinoma'. Further features of primary liver carcinoma are described by Wells[35] and Edmondson and Steiner.[11]

Age of Onset. Of the 95 cases reviewed by Bigelow and Wright,[5] 55 appeared under 2 years of age (58%), and in 35 (42%) the first symptoms developed at or before 1 year. Cases have been recorded in the neonatal period.[36,37]

Sex. Of the recorded cases 65 were males and 28 females, a ratio of nearly 2·3 : 1. In 2 cases the sex was not specified. The incidence of primary carcinoma of the liver in adult Bantus in the Union of South Africa is 7 times higher in males than in females,[4] but in the USA the sex incidence in adults is similar to that in infants.[11]

Race. Most reports in the literature fail to mention the race of the infant, but liver carcinoma in infants appears to occur equally in White and non-White races with a uniformly widespread geographical distribution.

Clinical Picture

Primary liver carcinoma in infancy usually runs a rapid course. The first sign is an enlargement of the abdomen and the development of a palpable mass in the upper abdomen. Attacks of pain over this area may occur. Jaundice is uncommon although a slightly raised serum bilirubin level may be found. The mechanical effects of pressure by the tumour on the bile ducts and the portal veins may give rise to an obstructive jaundice, ascites and signs of back pressure on the portal venous system. Anorexia, gaseous distension of the abdomen and loss of weight are common, but in some cases the infant appears well nourished. A swinging type of fever is not infrequent, especially in the closing stages of the illness. Anaemia of sufficient degree to call for a blood transfusion may be present. The average duration of life from the appearance of the first symptoms is about 4 months.

Diagnosis

The presence of a mass of fairly rapidly increasing size in the right upper quadrant of the abdomen presents certain diagnostic difficulties in an infant. If the mass is fairly large the clinical picture resembles a right-sided Wilm's tumour of the kidney, which is the provisional diagnosis commonly made. Yet primary carcinoma of the liver is not altogether an uncommon tumour in infancy and should always be considered in the differential diagnosis of lumps in the upper quadrant. Urine examination and a pyelogram is advisable in all cases. The tumour should not be palpated more than is necessary, since, in the case of a Wilm's tumour, frequent palpation may cause dissemination of malignant cells. Benign neoplasms and cysts of the liver and kidney, retroperitoneal teratoma, and neuroblastoma have to be considered. A pyelogram usually localizes a renal or adrenal tumour. The presence of calcification on the straight film of the abdomen strongly suggests a neuroblastoma, whilst the retroperitoneal teratoma can usually be felt extending deeply across the mid-line of the abdomen.

Enlargement of the liver may be due to a liver abscess as the result of an umbilical infection. Or an amoebic liver abscess may be present in an older infant or child, and amoebae may be found in a fresh stool. In the Union of South Africa parasitic cysts of the liver, usually due to echinococcus, should be considered and the Casoni skin test performed in suspected cases. Leukaemic infiltration of the liver may lead to gross hepatomegaly in young children without symptoms, and the diagnosis is dependent on a full blood examination. By and large, the diagnosis of primary liver carcinoma is one of exclusion with reliance on the history, symptoms and laboratory findings. Unfortunately, the recognition of the tumour is rare and it is usually large by the time it is discovered. Laparotomy is occasionally necessary in order to establish the correct diagnosis, although these infants tolerate laparotomy badly.

Prognosis

The disease is invariably fatal. One-third of the cases have metastases to other organs, notably to the lungs, lymph glands and adrenals.

Treatment

Treatment is palliative in nearly every case. Use of radioisotopes such as anhydrous chromic phosphate may give temporary benefit.[17] Radio-active iodinated human serum albumin, employed to detect secondary carcinomatous deposits in the liver, may have some therapeutic application.[27] The excision of liver tumours, benign or malignant, although fraught with many dangers, particularly the hazard of haemorrhage, is not impossible. Benson and Penberthy[2] removed a hamartoma in a 7-months-old infant, and several operators have removed malignant growths of the liver in adults successfully.[16,21,23] Reported cases of successful surgical removal are few and many appear, surprisingly, in the older literature; one wonders how reliable the reports on the histology were in these earlier cases. If on palpation the tumour appears to be single, and no evidence of secondary spread can be found, then laparotomy should be considered with the object of possible removal of the tumour.

DISCUSSION

Animal experimental work

It is difficult to evaluate the vast volume of experimental work in the production of liver carcinoma in animals, and to attempt to relate it to human liver carcinoma. Any correlation of the experimental work applies almost entirely to carcinoma in the adult and not in the infant.

Experimental carcinoma of the liver can be produced in rats by azo-compound dyes such as o-amino-azotoluene and p-dimethylamine azobenzene (butter yellow).[25] Riboflavin has been found to inhibit the speed with which azo-induced tumours appear, and cystine supplements to the diets containing the dye decreases the tumour incidence. The methionine antagonist, ethionine, when fed to rats, is also able to produce liver carcinoma[10], and other chemicals capable of doing this too are selenium, ethyl urethane, sodium

tannate, carbon tetrachloride, chloroform, thio-urea and alkaloids of senecio.

Cirrhosis

Many workers have shown that in susceptible strains of experimental animals the production of cirrhosis may lead to tumour formation. Evolution from gross fatty infiltration to diffuse hepatic fibrosis can be demonstrated by serial liver biopsies in rats fed on diets low in lipotrophic factors.[15] Rats on choline-deficient diets have been shown to go through the same stages, and finally to carcinoma.[6] It appears that in experimental animals certain dietary deficiencies are initiators of neoplasia.

Primary carcinoma of the liver is frequent in certain parts of the world where cirrhosis is common, and where nutritional deficiencies and parasitic infestation are often seen. The highest incidence is among the Bantu of Southern Africa and among Orientals.[4] It is the exception not to find cirrhosis in the African Bantu with liver carcinoma either in the form of diffuse hepatic fibrosis or nodular hyperplasia. That environmental rather than genetic causes are responsible is supported by the fact that the incidence is not nearly so high among American negroes. Also the incidence in Africa varies, primary liver carcinoma being 6 times commoner in East Coast Bantus than in those of the Union of South Africa.[4] The diets of the Bantu are low in protein and lipotrophic factors in many instances. If rats are fed on Bantu diets, 20% of them have been shown to develop fatty infiltration of the liver and, later, diffuse hepatic fibrosis.[14]

It appears therefore that cirrhosis with its nodular hyperplasia can be regarded as pre-cancerous. An over-all review of many thousands of cases of primary carcinoma of the liver from all parts of the world shows that about 50% of cases of primary liver carcinoma show histological evidence of cirrhosis.[25] That other factors are responsible is demonstrated by the relatively high incidence (7·3%) of carcinoma developing in patients with haemochromatosis.[5]

Virus Hepatitis

Primary liver carcinoma in adults can develop in livers which are the seat of post-infectious (viral) hepatic cirrhosis.[17,32] Infectious hepatitis *per se* is unlikely to be the immediate cause of liver carcinoma because epidemics of hepatitis have occurred in the USA without a corresponding increase in the incidence of liver carcinoma.[29]

Cirrhosis of the liver in infancy and childhood is caused by several agents,[7] and the group with obstructive jaundice, either congenital or due to specific viral hepatitis, gives rise to early and severe cirrhosis.[13] Yet the immediate cause of death is cirrhosis or its complications in these cases, and carcinomatous changes are rarely found supervening on the cirrhosis. However, Roth and Duncan[22] have recently described a White female child with primary liver carcinoma following giant-cell hepatitis acquired in infancy who died at the age of 2 years 9 months. Because of the increasing incidence of viral hepatitis seen in infants these authors suggest that a careful search be made for histological evidence of giant-cell hepatitis in all infants and children dying of liver carcinoma. Generally, the role of viral hepatitis in the causation of carcinoma of the liver in adults and infants is uncertain.

Kwashiorkor and Liver Fibrosis

In Southern Africa dietary shortage of protein is common among Coloured and Bantu infants and older children living in urban areas. At one extreme this may lead to the development of kwashiorkor, where the liver shows various degrees of fatty change. The study of the natural history of kwashiorkor has not borne out the theory of steady progression from a fatty liver to fibrosis,[33] which under the circumstances might conceivably lead to carcinoma of the liver in children. In a 5-year follow-up series Suckling and Cameron[28] found no case of hepatic fibrosis in liver biopsy specimens of 27 Coloured children from the Cape Town area treated for kwashiorkor (with the possible exception of one child). That a serious nutritional disorder, like kwashiorkor, among children seldom produces fibrosis of the liver, is highly significant. The analogy of liver injury in kwashiorkor and the induced fatty liver in rats breaks down at several points. There is a difference in response to treatment with choline and methionine.[34] There is also a difference in the site of the initial lesion. In the rat fatty infiltration and fibrosis begin in the centre of the lobule,[1] whereas in man they begin at the edge.[8] There is no good evidence that in man fatty infiltration is a precursor of cirrhosis.

A high percentage of African children in the territory along the river Gambia in British West Africa show degrees of peri-portal fibrosis, regardless of their nutritional status.[31] Stellate fibrosis is also found in livers of Native children in Uganda.[8,9] It is uncertain whether most of these are recovered fatty-liver cases, or whether they represent damage to the liver by associated disease, e.g. malaria or schistosomiasis. The latter is the more likely explanation. It should be noted, however, that in the areas mentioned kwashiorkor is also commonly seen. It will be an interesting undertaking to follow up these children into adult life with serial liver biopsies and see who will develop primary carcinoma of the liver.[29]

Age of Onset

The time interval for the sequence of cirrhosis or some other damaging agent to the liver developing into carcinoma is important at all ages. van Creveld[30] records the cases of 2 children who, surviving a prolonged time of dietary inadequacy and illness in infancy, were observed for 8-10 years, during which period they developed cirrhosis and finally carcinoma of the liver. The infant under 2 years of age has hardly the time to develop primary carcinoma of the liver when this has supervened on disturbance of the liver cell by damage, repair and regeneration. The only possible exception is the giant-cell hepatitis of infancy which becomes carcinomatous.[22] This form of hepatitis is believed to be caused by the virus of epidemic infectious hepatitis transmitted across the placenta during pregnancy from the blood of the mother who is a carrier.[13] There should be no difficulty in recognizing this condition by clinical, laboratory and histological studies.

In the majority of infants, there is no evidence either clinical or histological to suggest what factor or factors

are responsible for the development of malignant changes in liver cells.

SUMMARY

A case of primary carcinoma of the liver is reported occurring in a 4-months-old Coloured infant.

Primary liver carcinoma in infancy is rare and associated cirrhosis is unusual. The same tumour is very common in adult Bantus of Southern Africa, who have some form of cirrhosis present in most instances.

The pathology, clinical picture, diagnosis and management of liver carcinoma in infancy is described. The importance of early recognition is stressed, because at this stage, surgical removal may be possible despite the great technical difficulties such as haemorrhage.

The production of liver carcinoma in experimental animals by means of azo-compounds and other chemicals is briefly mentioned, as well as the possible role of cirrhosis, viruses and kwashiorkor in the aetiology of liver carcinoma in infants.

No convincing aetiological factors appear to be present in infants and the tumour is believed to represent a developmental dysplasia of liver cells originating *in utero*.

I wish to thank Dr. R. M. L. Kotze, Medical Superintendent of the Karl Bremer Hospital, Bellville, and Dr. W. Opie, Head of the Department of Paediatrics in the Medical Faculty of the University of Stellenbosch, for permission to publish this case. I am grateful to Dr. P. V. Suckling for his helpful criticisms in the preparation of the paper, to Dr. T. Mulligan for the histological reports, and to Mr. Robert Ellis for the photographs.

REFERENCES

1. Ashburn, L. L., Endicott, K. M., Daft, F. S. and Lillie, R. D. (1947): Amer. J. Path., **23**, 159.
2. Benson, C. D. and Penberthy, G. C. (1942): Surgery, **12**, 881.
3. Berk, J. E. and Lieber, M. M. (1941): Amer. J. Med. Sci., **202**, 708.
4. Berman, C. (1951): *Primary Carcinoma of Liver*. London: Lewis.
5. Bigelow, N. H. and Wright, A. (1953): Cancer, **6**, 170.
6. Copeland, D. H. and Salmon, W. D. (1946): Amer. J. Path., **22**, 1059.
7. Craig, J. M., Gellis, S. S. and Hsia, D. Y-Y. (1955): Amer. J. Dis. Child., **90**, 299.
8. Davies, J. N. P. (1948): Lancet, **1**, 317.
9. *Idem* (1952): Ann. Rev. Med., **3**, 99.
10. Editorial (1953): Nutr. Rev., **2**, 93.
11. Edmondson, H. A. and Steiner, P. E. (1954): Cancer, **7**, 462.
12. Gelfand, M. (1949): S. Afr. Med. J., **10**, 478.
13. Gellis, S. S., Craig, J. M. and Hsia, D. Y-Y. (1954): Amer. J. Dis. Child., **88**, 285.
14. Gilbert, C. and Gillman, J. (1944): Science, **99**, 398.
15. Gillman, J. and Gillman, T. (1943): Arch. Path., **40**, 239.
16. Lemmer, K. E. (1950): Arch. Surg., **61**, 599.
17. Low-Beer, B. V. A., Lawrence, J. H. and Stone, R. S. (1942): Radiology, **39**, 573.
18. Milman, D. H. and Grayzel, D. M. (1951): Amer. J. Dis. Child., **81**, 408.
19. Pirie, J. H. H. (1921): Med. J. S. Afr., **17**, 87.
20. Prates, M. (1940): S. Afr. Med. J., **14**, 95.
21. Quattlebaum, J. K. (1953): Ann. Surg., **137**, 787.
22. Roth, D. and Duncan, P. A. (1955): Cancer, **8**, 986.
23. Schottenfeld, L. E. (1955): Amer. J. Dig. Dis., **22**, 139.
24. Sheldon, W. H. and James, D. F. (1948): Arch. Intern. Med., **81**, 666.
25. Sherlock, S. (1955): *Diseases of the Liver and Biliary System*. Oxford: Blackwell.
26. Steiner, M. M. (1938): Amer. J. Dis. Child., **55**, 807.
27. Stirrett, L. A., Yuhl, E. T. and Libby, R. L. (1953): Surg. Gynec. Obstet., **96**, 210.
28. Suckling, P. V. and Cameron, J. A. H. (1957): J. Trop. Med. Hyg., **4**, 173.
29. Unio Internationalis contra Cancrum (1957): Acta. Un. Ent. Cancr., vol. 13, Nos. 4-5.
30. van Creveld, S. (1952): Ned. T. Geneesk., **96**, 3234.
31. Wainwright, J. and Roach, G. G. (1957): South Afr. Canc. Bull., **4**, 162.
32. Walshe, E. M. and Wolff, H. H. (1952): Lancet, **2**, 1007.
33. Walters, J. H. and Waterlow, J. C. (1954): *Fibrosis of Liver in West African Children*. Spec. Rep. Ser. Med. Res. Coun. (London), No. 285.
34. Waterlow, J. C. (1949): Trans. Roy. Soc. Trop. Med. Hyg., **42**, 416.
35. Wells, H. G. (1940): Arch. Path., **30**, 535.
36. Widenhofer (1859). Quoted by Steiner, *loc. cit.*[35]
37. Wilbur, D. L., Wood, D. A. and Willet, F. M. (1944): Ann. Intern. Med., **20**, 453.