THE SPALLING AND MIGRATION OF
SILICONE FROM BLOOD PUMP TUBINGS
IN HAEMODIALYSIS PATIENTS

ANTHONY SIEW-YIN LEONG
DEPARTMENT OF MEDICINE
THE UNIVERSITY OF ADELAIDE

THESIS SUBMITTED TO THE UNIVERSITY OF
ADELAIDE FOR THE DEGREE OF
DOCTOR OF MEDICINE

December, 1981
CONTENTS

Summary 1
Contributions of this Thesis 4
Acknowledgements 6

I. INTRODUCTION 7

II. MORPHOLOGICAL CHARACTERISTICS OF A FOREIGN MATERIAL IN THE LIVER 9

II.a. Light Microscopy
II.b. Polarisation Microscopy
II.c. Phase Contrast Microscopy
II.d. Electron Diffraction Studies
II.e. Electron Microscopy
II.f. Summary

III. MATERIAL AND METHODS 15

III.a. Material Examined
   - Antemortem Material
   - Postmortem Material
   - Controls
III.b. Methods

IV. DISTRIBUTION AND TISSUE REACTION TO THE FOREIGN MATERIAL 20

IV.a. Light Microscopic Observations
   - Liver Pathology
   - Splenic Pathology
- Lymph Node Pathology
- Bone Marrow Pathology
- Pulmonary Pathology
- Other Tissues

IV.b. Electron Microscopic Observations
- Ultrastructural Observations in the Liver
- Ultrastructural Observations in the Spleen

V. PRELIMINARY ANALYSIS OF THE FOREIGN MATERIAL

V.a. Literature Review
- Granulomatous Hepatitis
- Hepatitis in Renal Patients
- Particulate Contamination in Haemodialysis
- Methods of Identification of Particulate Material

V.b. Consultation and Preliminary Analysis
- Electron Dispersive X-Ray Analysis
- Gas Chromatography-Mass Spectrometry Analysis
- Examination of Effluent Blood from Haemodialysis Machines

VI. ANIMAL EXPERIMENTS

VI.a. Intravenous Injection of PVC and Silicone

VI.b. Subcutaneous Introduction of Silicone Particles

VII. DEFINITIVE IDENTIFICATION OF FOREIGN MATERIAL

VII.a. Morphologic Examination of Silicone Mastitis
VII.b. Electron Dispersive X-Ray Analysis of the Foreign Material
VII.c. Atomic Absorption Spectrometry Analysis of the Foreign Material

VIII. CLINICO-PATHOLOGIC CORRELATION

VIII.a. Analysis of Clinical Data
VIII.b. Statistical Analysis of Histologic Quantitative Studies
VIII.c. Examination of Sequential Biopsies

IX. IN VITRO SPALLATION TESTS

IX.a. Atomic Absorption Spectrometry Analysis
IX.b. Scanning Electron Microscopy

X. DISCUSSION

X.a. The Chemistry of Silicone
X.b. Experimental Toxicity of Silicone
X.c. Medical Usage of Silicone
X.d. Clinical Complications of Silicone Usage
X.e. The Pathology of Silicone Migration in Haemodialysis Patients
X.f. Sequel to the Identification of Silicone-Induced Chronic Hepatitis
X.g. Conclusions

APPENDICES

BIBLIOGRAPHY
SUMMARY

This study was instituted following the observation of an unsuitable, refractile, non-birefringent material in liver biopsy specimens from renal patients. Retrospective examination of tissues from selected clinical populations and suitable controls revealed that the material was present only in patients treated with repeated haemodialysis. Of 38 haemodialysed patients who had liver biopsies, 12 showed varying amounts of the material. Of 31 haemodialysed patients who came to autopsy, 22 showed accumulations of the contaminant. The substance had embolised in the blood and was engulfed by macrophages and stored in the mononuclear phagocytic system. Disseminated granulomata were present in the liver, spleen and lymph nodes. The ultrastructural appearances were characteristic and very suggestive of a plastic-like substance. The particles were found to be located in macrophage lysosomes. Filings from new silicone tubing from the roller pump segment of the haemodialysis machine introduced subcutaneously into rats produced a granulomatous response with particulate inclusions of a similar light and electron microscopic appearance.

Local and overseas consultation did not help identify the material. After initial setbacks the contaminant was confirmed to be silicone by electron dispersive X-ray analysis and back-scattered electron imaging. The analysis of silicone in small quantities is fraught with problems. Atomic absorption spectrometry allowed quantitation of silicone in several autopsy tissue samples. Detectable quantities were found in the liver, spleen, lymph node and other organs. The accumulation of hepatic silicone correlated with the duration of exposure. A positive correlation could also be demonstrated between the amount of silicone and the severity of hepatic fibrosis and inflammation. Seventeen biopsy and 10 autopsy cases with hepatic
deposits of silicone showed raised levels of serum aspartic transaminase (AST), and eight autopsy cases had normal levels of this enzyme. Eleven patients showed elevations of serum AST which exceeded a six-month duration (chronic hepatitis). After consideration and exclusion of other known causes of chronic hepatitis, it was felt that silicone-induced hepatitis was a possible cause of chronic liver dysfunction in the haemodialysed patient.

Silicone or polydimethylsiloxane is widely employed in medicine, pharmacy, and cosmetics. Despite its stability and relative physiological inertness there is ample experimental and clinical evidence to indicate that it can induce a chronic inflammatory response. Subcutaneous injections of fluid silicone in the rat evoked an initial inflammation which lasted up to six months. Subsequent examination revealed fibrous encapsulation of the deposit with pericellular macrophages, lymphocytes and giant cells. Massive localised doses of silicone produced striking abnormalities of adipose tissue throughout the body and the material was dispersed in many organs. The fibrogenic and inflammatory properties of silicone have also been seen in clinical situations. Silicone mastitis is a chronic granulomatous reaction around deposits of silicone fluid, gel or elastomer introduced for breast augmentation. Migration of the material produces a granulomatous inflammation in draining lymph nodes. Illicit injections of silicone have produced disseminated granulomatosis. In such cases elevated levels of serum hepatic enzymes have been recorded in association with granulomatosis in the liver. Reports of fatal and near-fatal allergic-type responses to silicone elastomer prostheses and subcutaneous injections have described a febrile systemic illness associated with diffuse arthritis, renal failure and an adult respiratory distress syndrome. Other examples of clinical migration of silicone with production of disseminated granulomatosis include the decay and fragmentation of silicone balls in ball-valve cardiac prostheses. The migration of silicone from orthopaedic prostheses has also produced granulomatosis in the adjacent synovium and draining lymph nodes. In all these instances refractile particles were observed in phagocytic cells.
The presence of silicone in the liver of our patients was consistently associated with fibrosis whereas inflammation was variable. Experimental studies indicate that silicone initiates an inflammatory response which subsides as fibrosis supervenes and isolates the foreign material. It is suggested that this phasic reaction pattern might be reflected as variations in serum AST levels.

While there is strong evidence to show that silicone might be a primary etiologic factor in the causation of chronic hepatitis, it is possible that silicone may also function in a synergistic manner to prolong hepatic inflammation and dysfunction initiated by other causes. In the presence of depressed erythropoiesis and impaired immune function which commonly accompanies chronic renal failure, it was not possible to fully evaluate any functional effects that silicone deposition may have had in the bone marrow, spleen and lymph nodes.

Finally, the source of silicone spallation was proven by in vitro testing of new silicone tubings. Fragmentation of the inner walls of the tubing was demonstrated by scanning electron microscopy and atomic absorption spectrometry of the effluent blood. It is strongly recommended that this source of contamination in extracorporeal circulation be immediately replaced.