MULTIPLE PULMONARY EMBOLI FOLLOWING ARTIFICIAL HIBERNATION WITH HYPOTHERMIA

REPORT OF A CASE

BY

RONALD S. LAMBIE, M.R.C.S., L.R.C.P.

Chief Resident, Department of Anesthesiology

LESTER G. JOSEPH, M.D.

Consultant in Cardiology

AND

GEORGE WILSON, M.D.

Chief Resident, Department of Thoracic Surgery

Hospital of St. Raphael, New Haven, Connecticut

Recently we have had a patient with carcinoma of the cardia of the stomach which was present in a hiatal hernia. A transthoracic oesophago-gastrectomy was performed in which "artificial hibernation" with hypothermia was used, the technique employed being a modification of that described by Huguenard (1953). Following this procedure multiple pulmonary emboli developed, and in this paper some of the factors which may have predisposed to this complication are discussed.

Case History

A 76-year-old white man was admitted to the Hospital of St. Raphael on January 4, 1955, with the chief complaint of dysphagia and vomiting of five months' duration. He was weak and had recently lost 50 lb. (22.7 kg.) in weight. His history revealed that in 1920 he was admitted to another hospital because of "stomach trouble," though gastro-intestinal investigation gave normal findings. He remained in fairly good health until 1948, when he was admitted to this hospital with nausea, vomiting, and severe anterior left chest pain radiating to the left shoulder. He was then found to have a para-oesophageal hiatus hernia with half the stomach in the left thoracic cavity.

He continued in good health until five months before the present admission, when a barium x-ray study confirmed the hiatus hernia with the possibility now of a carcinoma of the lower end of the oesophagus or the cardia of the stomach. His temperature was 99° F. (37.2° C.), pulse 64, respirations 20, and blood pressure 108/70 mm. Hg in both arms. The skin was dry with loss of turgor. The chest was emphysematous and had an increased antero-posterior diameter. The heart was normal. Abdominal examination was negative except for a liver edge palpable two fingerbreadths below the right costal margin; this was smooth without evidence of nodularity. On rectal examination the prostate appeared firm and without nodularity. Laboratory investigation showed: non-protein nitrogen, 31 mg. per 100 ml.; fasting blood sugar, 88 mg. per 100 ml.; urine normal; haemoglobin, 11.5 g. per 100 ml.; haematocrit value, 39%; W.B.C., 3,500 per c.mm. (differential count normal); prothrombin concentration, 61%. Blood chemistry (in mEq.) was: sodium 135.4, potassium 4.4, carbon dioxide 25.8, and chlorides 106. An electrokymogram was normal.

On January 6 oesophagoscopy revealed a lesion, situated 37 cm. from the incisural ridge, which on biopsy proved to be an adenocarcinoma of the stomach. In preparation for the removal of this he was given whole-blood transfusions to restore his blood volume and at the same time fluid intake was maintained.

Operation

A transthoracic oesophago-gastrectomy was performed on January 10 under "artificial hibernation" with hypothermia. The procedure was as follows. The previous night the patient was given "thorazine" (chlorpromazine), 100 mg., pethidine, 50 mg., and atropine, 0.3 mg., intramuscularly. At 7.30 a.m. two infusions were started—one consisting of 1,000 ml. of 5% glucose in water, and the other of 250 ml. of normal saline solution, the latter being the vehicle for the "lytic cocktail." Anaesthesia was induced with 2.5% thiopentone sodium, 6 ml. intravenously, and maintenance was by 1 litre of oxygen and 2 litres of nitrous oxide. At 7.45 a.m. he was given promethazine, 50 mg. intramuscularly, and the "lytic cocktail," composed of diethazine, 50 mg., pethidine, 10 mg., and chlorpromazine, 25 mg. Hypothermia was induced by covering the entire body with small bags of crushed ice. No shivering occurred. Endotracheal intubation was performed and oxygen given through a closed circuit. Pulmonary ventilation was assisted with intermittent positive pressure of 12 cm. of water.

At 8.45 a.m. the "lytic cocktail" was repeated; the ice-bags were removed when the temperature reached 91.4° F. (33° C.), and surgery started at 9.30 a.m. During the operation "arfonad,"* 5 mg., was given by intravenous injection. This was followed in ten minutes by a drop in blood pressure to 60/30 mm. Hg, but the systolic pressure gradually returned to 100 mm. within the next hour. Meanwhile the body temperature slowly fell to reach its lowest level of 83.3° F. (28.5° C.), where it remained for two and a half hours. Respiratory acidosis was avoided by the adequate ventilation. There was no change in the electrocardiographic picture during the entire procedure. Electrolytes, determined before, during, and after the operation, remained within normal limits, and the total operating time was six hours. The estimated blood loss was 600 ml. The patient was rewarmed slowly over a period of seven hours and all vital signs were normal.

Post-operative Course

The immediate post-operative course was uneventful. A Levin tube was placed in the stomach through the anastomosis, and maintenance was by nasal oxygen, intravenous therapy, and chest suction. On the second post-operative day the lungs were completely expanded and chest suction was discontinued. The Levin tube was removed on the third day and small quantities of water were given by mouth. By this time the patient could walk with assistance. His sutures were removed on the seventh day; the wound was clean and well healed. He gradually improved until the evening of January 26, when he suddenly went into shock. Despite administration of noradrenaline (which promptly restored his blood pressure), nikethamide, and oxygen his condition rapidly deteriorated and he died 36 hours later.

Post-mortem Appearances

Necropsy was performed by Dr. R. R. Nesbit, pathologist to the hospital. Only the findings in the lungs will be described here.

The right lung weighed 710 g., and the left 640 g. The pleural surfaces were glistening and smooth. From the cut surface a large amount of frothy fluid escaped. Both lungs were subcrepitant; the upper lobes were tan to yellow and the lower lobes mottled dark red to blue. The pulmonary artery with its branches in both lungs was filled with finger-like, extending thrombi. These were composed of layers varying in colour from yellow to pinkish red; they were not attached to the vessel walls and were easily extracted. Their age ranged from 48 hours to three weeks. The pleural surface was thickened owing to the formation of fibrous tissue. The alveoli varied greatly in size and the general picture was one

*Arfonad is D-3:4-(1':3'-dibenzyl-2'-ketoimidazolido)-1:2-trimethylene thiophanium D-camphor sulphonate.

of dilated and confluent alveoli. The alveolar spaces were completely free in some areas; others contained scattered erythrocytes and macrophages and some precipitated albuminous material; while still others were filled with an acute inflammatory exudate composed mostly of polymorphonuclear leucocytes, with erythrocytes, macrophages, and definite fibrin webs.

Discussion

Because of the patient's general condition—his age was 76; he had suffered a recent weight loss of 50 lb. (22.7 kg.); he had moderately severe fibrosis and emphysema of the lungs and generalized arteriosclerosis—and since it was anticipated that operation would last six hours, it was felt that this case was suitable for artificial hibernation with hypothermia. Also, Huguenard (1953) has stated that chronic pulmonary disease does not constitute a contraindication but rather an indication for this procedure. Laboratory findings and an electrokymogram were similar to those reported by Huguenard. The only electrocardiographic changes noted were non-specific T-wave changes in the immediate post-operative period. These were interpreted as probably positional in origin. The electrolyte values remained within normal limits throughout. A transient hyperglycaemia (up to 250 mg. per 100 ml.) occurred at the end of the operation, but the blood sugar returned to a normal level on the first post-operative day. Dundee (1954) questioned whether this could be due to a direct toxic effect of chlorpromazine on the liver.

The microscopic findings would seem to indicate that pulmonary infarction had occurred some time previously as well as recently. It is interesting to speculate on what may have been the cause of these infarcts. A systolic blood pressure of 60 mm. Hg may be a factor. However, Zeavin *et al.* (1954) are of the opinion that this hypotension is physiological in that it is accompanied by a marked reduction in oxygen requirement. Another factor may have been the prolonged collapse of the left lung during surgery. Deterling *et al.* (1955) have shown that during hypothermia there is an increase in the clotting time of the blood, but no increase in bleeding because of the slowed peripheral circulation. From the findings of the above authors it would appear that slowing of the circulation does not predispose to the formation of emboli. Huguenard warns of the "rebound" that takes place during the rewarming period, and urges the use of heparin. In the present case heparin was not used in the rewarming period, as it was considered that bleeding might occur from the site of anastomosis. Nevertheless recovery was uneventful until the sixteenth day after operation, when signs and symptoms of shock appeared. Despite energetic treatment the patient died 36 hours later.

At necropsy pulmonary emboli were found, but it is difficult to be sure what were the factors, if any, predisposing to this complication. Therefore it is suggested that to guard against such an eventuality anticoagulant therapy be used, not only in the rewarming period, but also post-operatively.

Summary

A case is presented in which oesophago-gastrectomy was performed with the use of "artificial hibernation" with hypothermia. This procedure was complicated post-operatively by the development of multiple pulmonary emboli. It is suggested that anticoagulant therapy should be used in the post-operative period as well as in the rewarming period to prevent this complication.

REFERENCES

- Deterling, R. A., Nelson, E., Bhonslay, S., and Howland, W. (1955). *Arch. Surg. (Chicago)*, 70, 87.
Dundee, J. W. (1954). *Brit. J. Anaesth.*, 26, 357.
Huguenard, P. (1953). *Anesth. et Analg.*, 10, 16.
Zeavin, I., Virtue, R. W., and Swan, H. (1954). *Anesthesiology*, 15, 113.

EFFECT OF ADDED TOXOIDS ON THE ANTIGENICITY OF *H. PERTUSSIS* VACCINES

BY

J. UNGAR, M.D., D.C.P.

From the Glaxo Laboratories Ltd., Greenford, Middlesex

It has been firmly established that the addition of *Haemophilus pertussis* vaccine to diphtheria and tetanus toxoids enhances the activities of both antigens (Greenberg and Fleming, 1947). Addition of mineral carriers—for example, aluminium phosphate—to the toxoids for the immunization of children can be replaced by the addition of *H. pertussis* (Ungar, 1952, 1954). The pronounced local reaction after inoculations with antigens containing mineral carrier is thus avoided. Earlier work by Glenney and Waddington (1928), and more recent work by Barr and Llewellyn-Jones (1953), indicated that the qualitative and quantitative composition of the components in a combined prophylactic might influence in animals the degree of immunological response to the different components. Under a particular set of conditions those authors noticed that one component had interfered with the immunity response to the other antigens present in a combined product.

In view of the present general interest in combined prophylactics for the immunization of children we have investigated whether or not the presence of either toxoid, diphtheria or tetanus, or of both, reduced the immunity response of mice to *H. pertussis* vaccines. Combined antigens that had been used for the immunization of children, with compositions based on earlier experiments on animals, were chosen.

Experimental

Two series of prophylactics were prepared by adding toxoids to each of two *H. pertussis* vaccines A and B, prepared on different occasions but otherwise similar. The following prophylactics were used:

- (1) *H. pertussis* vaccine A $20,000 \times 10^6$ cells/ml.
- (2) *H. pertussis* vaccine A plus diphtheria toxoid 25 Lf/ml.
- (3) *H. pertussis* vaccine A plus diphtheria toxoid 25 Lf/ml., plus tetanus toxoid, 2.5 Lf/ml.
- (4) *H. pertussis* vaccine B $20,000 \times 10^6$ cells/ml.
- (5) *H. pertussis* vaccine B plus diphtheria toxoid 25 Lf/ml.
- (6) *H. pertussis* vaccine B plus diphtheria toxoid 25 Lf/ml., plus tetanus toxoid, 2.5 Lf/ml.

The *H. pertussis* vaccines were prepared from freshly isolated strains grown on Bordet-Gengou medium, killed with formalin and preserved in thiomersalate ("merthiolate") (1:7,500). The diphtheria and tetanus components added were plain toxoids, purified by ammonium sulphate precipitation.

The six products were tested three times concurrently for their ability to protect mice against intracerebral challenge by Kendrick's method (Kendrick *et al.*, 1947), the antigenic ratios being assessed by the method of Weiss (1948). The mice used were of both sexes, from the colony of strain A2G mice inbred in these laboratories.

Similar mouse protection tests were carried out on a series of 12 plain *H. pertussis* vaccines, prepared from organisms grown for 48 hours on Bordet-Gengou medium, killed with formalin and standardized to $20,000 \times 10^6$ cells per ml. by opacity measurement. The results of these tests were compared with those on 16 different batches of a diphtheria-pertussis-tetanus prophylactic ("triple antigen" D.P.T.), prepared by the addition of both toxoids to