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# HYPERBARIC OXYGEN IN THE RESUSCITATION OF THE NEWBORN

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IN 1928, Henderson wrote: " The first quarter of an hour after birth is the most dangerous period of life. Its mortality is as great as that of any subsequent month. No single discovery in medical science or improvement in practice could do more to save lives than would measures to avoid the losses that now occur within a few minutes after birth." The relative danger of the first quarter of an hour has greatly increased since 1928 as the mortality during the rest of infancy has steadily fallen. The Perinatal Mortality Survey carried out in Britain in 1958, under the auspices of the National Birthday Trust Fund, revealed that 30% of all perinatal mortality (stillbirths plus deaths during the first week) was the result of asphyxia during labour in babies who were otherwise mature and normal (*Lancet* 1962).

There is little doubt that deaths from asphyxia neonatorum could be considerably reduced if modern methods of resuscitation, particularly tracheal intubation and intermittent positive-pressure inflation of the lungs, were more efficiently practised in our hospitals (Barrie 1963). None the less, those experienced in such techniques are well aware of their limitations and dangers. It is often impossible to achieve expansion of the atelectatic lungs, and there is doubt as to the maximum intratracheal pressure which may safely be employed to gain this objective. Even the premature infant can produce negative intrathoracic pressures of 40 cm. of water during his first gasp (Donald 1957). This pressure, necessary to overcome the cohesion of the alveoli, is safe only because it is so briefly sustained. But if the pædiatrician produces an intratracheal pressure of this degree, in his attempts to flood the circulation with oxygen and to expand the lungs, he runs the risk of rupturing the lung by sustaining the pressure for too long.

It occurred to us that hyperbaric oxygen might provide oxygen in readily available form which would be introduced into the circulation and carried to the tissue fluids of the central nervous system. We had previously shown that hyperbaric oxygen can relieve hypoxia in the respiratory distress syndrome (R.D.S.) of the newborn (Hutchison et al. 1962). Although this was found to be ineffective in R.D.S., because it failed to relieve respiratory acidosis, a similar effect on the hypoxia of apnœa neonatorum might have happier results.

## Physiological Basis

In the apnœic newborn infant the hæmoglobin is grossly undersaturated and the pulmonary alveoli are collapsed and airless. This means that the normal route for oxygen into the circulation is blocked. If the hypoxic infant is totally immersed in pure oxygen at 2–4 atmospheres of pressure there will be a steep gradient of 1500–3000 mm. Hg between the environment and his plasma and tissue fluid. Under such circumstances the oxygen diffusing into the circulating blood via the mucous membranes, including those of the respiratory tract, will increase considerably. There is also increasing evidence, confirming earlier work (Petrun 1961), that under these conditions the skin may act as an important route of entry for oxygen (Williams 1963).

This means that under such circumstances hyperbaric oxygen is being used for a different purpose than in the cases so far reported (Boerema 1961, Illingworth et al. 1961). In the latter, hyperbaric oxygen is used primarily to increase the quantity of oxygen in solution in the plasma, and to increase the oxygen tension in the blood. In the cases now reported, the prime purpose of hyperbaric therapy is to force oxygen into the unsaturated blood and so correct the severe hypoxia. The oxygen will be taken up by the reduced hæmoglobin of the infant, and it is unlikely (until respiration is established) that there will be sufficient to increase the oxygen tissue tension to levels above those of a normal infant.

## Apparatus and Methods

The pressure-oxygen equipment (fig. 1) was designed by the medical team and constructed by the engineering division of the Vickers Group Research Establishment. It was built in 1960 to investigate the therapeutic effects of high-pressure oxygen on the neonate, and it was developed from the larger chamber designed for use with adults (Emery et al. 1960).

The chamber is a double-skinned ' Perspex ' cylinder with metal end-caps. One end-cap opens to allow the infant to be positioned on the sliding stretcher. The other end-cap contains a number of electrical connections for the monitoring leads. The maximum working pressure is 45 lb. per sq. in. (4 atmospheres absolute), and the rate of compression and decompression can be varied up to 8 lb. per sq. in. per min. There is a constant volume-flow of oxygen through the chamber at 7 litres per min., and this prevents any build-up of carbon dioxide.

In the most recent cases certain electrophysiological monitoring was carried out. Before being placed in the chamber, these infants had standard electrocardiogram (E.C.G.) leads attached to their limbs and a small transducer for monitoring respiratory movements was strapped round the chest. The E.C.G., heart-rate, and respiratory rate were recorded on a four-channel Kelvin Hughes 2B recorder at a speed of 2·5 cm. per sec. A small, transistorised, low-frequency, alter-

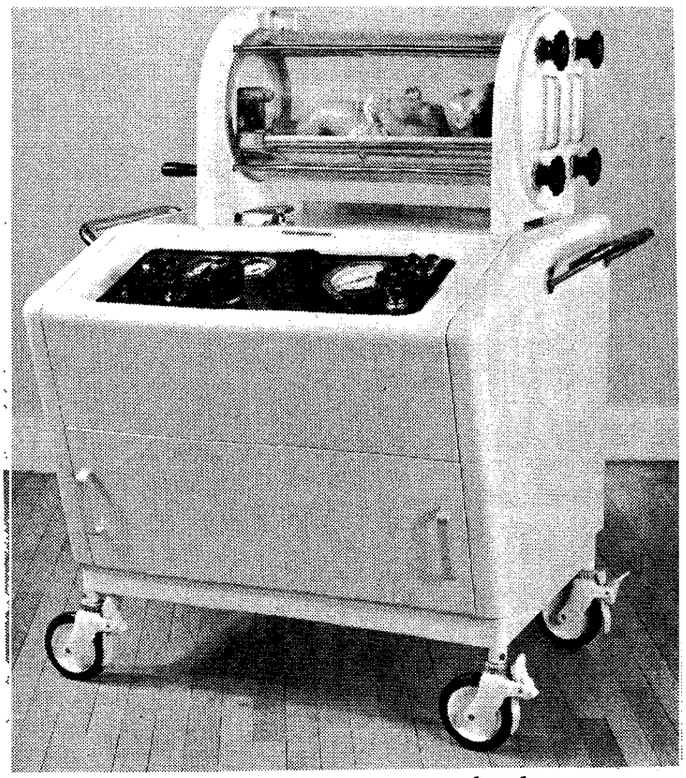

Fig. 1—High pressure oxygen chamber.

nating-current coupled amplifier, with a gain of 68 decibels, was used for the E.C.G. The heart-rate counter selected the R-waves from the E.C.G. and passed them via a pulse-shaping circuit to a monostable vibrator. The resulting pulse was integrated to give a voltage proportional to heart-rate, and this voltage was measured on a calibrated meter. The counter and the recorder operated over two ranges of 30–150 and 120–240 min., with a built-in calibration unit for 60, 120, 180, and 240 beats per min. Respiratory rate was measured by means of a resistive strain-gauge transducer feeding directly to the recorder amplifier. Unfortunately this recording was associated with considerable technical difficulties. The Apgar score (Apgar et al. 1958) was recorded at the time of placing the infant in the pressure chamber.

An infant was placed in the pressure chamber only when the usual conservative methods of resuscitation had failed. These included pharyngeal and nasal suction, the administration of oxygen by plastic funnel, and the oral or intravenous use of analeptics such as vanillic acid diethylamide ('Vandid') or nikethamide. Nalorphine hydrobromide was given when indicated. In some of the earlier cases (9) tracheal intubation and intermittent positive-pressure respiration were also used unsuccessfully before resort was had to hyperbaric oxygen.

Compression was started as soon as the infant was in the chamber. The pressure was raised at the maximum rate to 2 atmospheres absolute (15 lb. per sq. in. gauge). If there was no improvement at this stage the pressure rise was allowed to continue, up to the maximum of 4 atmospheres absolute (45 lb. per sq. in. gauge). If necessary the pressure was held at intermediate level. The effects were usually dramatic. Within a few minutes the cyanosis and pallor of asphyxia pallida gave way to a gratifying pink, and the heart-rate increased. Intermittent gasps were followed by true respiratory movements. Limpness was replaced by kicking and often crying. The picture of the apparently dead infant trying to "fight his way" out of the chamber after a few minutes was sometimes most impressive. Decompression was started (eight minutes from 4 atmospheres) as soon as respiration seemed to be established, and the infant was then transferred to an incubator. The maximum time under pressure was thirty minutes, although some infants (14) were compressed more than once owing to subsequent deterioration in their condition.

TABLE I—ANALYSIS OF 16 CASES IN WHICH SUCCESSFUL RESUSCITATION WAS FOLLOWED BY DEATH MORE THAN SIX HOURS LATER

| Birth-weight (kg.) | Age at com-pression (min.) | Apgar score | Age at death | Necropsy findings |
|---|---|---|---|---|
| 0·76 | 5 | Not recorded | 3 days, 10 hr., 50 min. | Intrauterine pneumonia, placentitis |
| 1·62 | 25 | Not recorded | 1 day, 20 hr., 55 min. | I.C.H., tentorial tears, pneumonia |
| 3·85 | 15 | 3 | 4 days, 23 hr., 25 min. | Myelocele, hydrocephalus |
| 1·05 | 5 | 2 | 13 hr., 20 min. | Hyaline membrane, cerebellar hæmorrhage |
| 1·21 | 7 | 1 | 20 hr., 20 min. | Hyaline membrane, I.V.H. |
| 2·66 | 8 | 3 | 22 hr., 23 min. | Pulmonary hæmorrhage |
| 1·31 | 3 | 2 | 14 hr., 15 min. | Hyaline membrane |
| 1·98 | 9 | 1 | 12 hr., 10 min. | Hyaline membrane, I.V.H. |
| 1·23 | 15 | 2 | 3 days, 22 hr., 20 min. | Pneumonia |
| 3·06 | 10 | 2 | 18 hr., 25 min. | Meconium aspiration, pneumothorax |
| 3·73 | 25 | 4 | 12 hr., 25 min. | Meconium aspiration, pneumonia |
| 1·69 | 5 | 1 | 1 day, 19 hr., 10 min. | Intrauterine pneumonia, pneumothorax |
| 1·53 | 38 | 4 | 7 hr., 20 min. | Hyaline membrane |
| 0·78 | 25 | 2 | 10 hr., 20 min. | Hyaline membrane, immature lungs |
| 2·22 | 7 | 3 | 2 days, 3 hr., 45 min. | Hyaline membrane, I.V.H. |
| 1·30 | 20 | 2 | 6 hr., 45 min. | Hyaline membrane, I.V.H. |

TABLE II—ANALYSIS OF 14 CASES IN WHICH RESUSCITATION FAILED OR IN WHICH INFANTS DIED WITHIN SIX HOURS

| Birth-weight (kg.) | Age at com-pression (min.) | Apgar score | Age at death | Necropsy findings |
|---|---|---|---|---|
| 3·24 | 25 | Not recorded | 3 hr., 5 min. | Primary atelectasis |
| 3·94 | 17 | 1 | 35 min. | I.C.H., bilateral, tentorial tears |
| 3·56 | 15 | 2 | 2 hr., 35 min. | Pulmonary and adrenal hæmorrhage |
| 2·76 | 28 | 2 | 55 min. | Primary atelectasis, pulmonary hæmorrhage |
| 1·34 | 10 | 3 | 4 hr., 55 min. | No necropsy; clinical R.D.S. |
| 2·01 | 2 | 1 | Stillborn | No necropsy |
| 4·09 | 12 | 1 | 55 min. | Meconium aspiration |
| 3·88 | 10 | 1 | Stillborn | Primary atelectasis, placental insufficiency |
| 0·90 | 25 | 2 | 1 hr., 5 min. | Primary atelectasis, immature lungs |
| 1·50 | 10 | 1 | Stillborn | Primary atelectasis, placentitis |
| 2·63 | 10 | 1 | Stillborn | I.C.H., tentorial tears, pneumothorax |
| 0·87 | 4 | 1 | 1 hr., 30 min. | Hæmolytic disease |
| 3·65 | 5 | 1 | Stillborn | I.C.H. |
| 1·41 | 5 | 1 | Stillborn | Intrauterine pneumonia |

## Results

65 infants with apnœa neonatorum have been treated. The results, and the proportions of mature and premature infants, are:

| | *Premature* | *Mature* | *Total* |
|---|---|---|---|
| Survived .. .. .. .. | 13 | 22 | 35 |
| Died after six hours .. .. .. | 12 | 4 | 16 |
| No response or died within six hours | 6 | 8 | 14 |

Thus 35 (54%) were discharged apparently well, 16 (25%) appeared to respond successfully but died after six hours from a variety of causes, and 14 infants (21%) did not respond or responded initially only to die within six hours. The 16 cases of successful resuscitation in which death ensued after six hours are analysed in table I. 12 of these deaths were in premature infants; none could have been attributed to hyperbaric oxygen. Of the 14 cases in which resuscitation failed, 6 were stillborn, 3 were premature, and 4 had lesions other than primary atelectasis, so that in all but 1 infant there was an adequate explanation of the failure. It will be noted in tables I and II that 3 infants died with pneumothorax. All of these were subjected to tracheal intubation only after hyperbaric oxygen had failed to produce any response, and it will also be noted that in each case there were additional serious pathological

changes. The Apgar score, recorded at the onset of compression in 57 of the 65 cases, was:

| *Apgar score* | *Total cases* | *Survived* | *Died after six hours* | *Died before six hours* |
|---|---|---|---|---|
| 1 | 13 | 1 | 3 | 9 |
| 2 | 20 | 11 | 6 | 3 |
| 3 | 12 | 8 | 3 | 1 |
| 4 | 7 | 5 | 2 | .. |
| 5 | 3 | 3 | .. | .. |
| 6 | 2 | 2 | .. | .. |

The prognosis bore the expected close relationship to the Apgar rating. Of the 35 surviving infants the idiopathic R.D.S. developed in 3, but with appropriate treatment they recovered (Hutchison et al. 1962). A few infants exhibited signs of cerebral " irritation " for the first few days but none had frank convulsions or any signs to suggest oxygen poisoning. When compression is in pure oxygen there is, of course, no danger of caisson disease. Retrolental fibroplasia is extremely unlikely with the short periods of compression used in the case of severely anoxic infants.

### Illustrative Case-reports

**Case 1.**—The mother, aged 39, had had two previous miscarriages, and she was known to have a double uterus. Her membranes ruptured at thirty-seven weeks' gestation. Cæsarean section was performed under general anæsthesia six hours later. A female infant, weight 2·89 kg., was born in a state of asphyxia pallida. She gasped once and showed no further response to facial oxygen or intravenous nikethamide. She was placed in the pressure chamber, and compression was started at the age of 11 minutes, when the Apgar score was 1. Two minutes later she gasped, and her colour became good. Regular respiration started after five minutes, when the pressure was held at 20 lb. per sq. in. Decompression was started after seven minutes in the chamber. Her future progress was uneventful apart from a short period of irritability between eighteen and twenty-four hours after birth.

**Case 2.**—The mother, aged 18, had had a previous miscarriage. Her membranes ruptured spontaneously at thirty weeks' gestation. Labour started twenty-four hours later, and a male infant, weight 1·95 kg., was spontaneously delivered by the vertex after a labour of six hours and fifty minutes. He remained completely apnœic despite pharyngeal suction and facial oxygen. He was placed in the pressure chamber, and compression was started at the age of 5 minutes. At that time the heart-rate was 45 per min. (fig. 2*a*) and the Apgar score was 2. The first gasp occurred after twenty-four seconds in the pressure chamber. Cyanosis had gone after two minutes. After seven minutes the heart-rate was 120 per min. (fig. 2*b*). Regular respiration was only established after sixteen minutes and twenty seconds of compression, when the heart-rate had risen to 150 per min. (fig. 2*c*). Decompression from 45 lb. per sq. in. was started after nineteen minutes. The infant had a few cyanotic attacks in his incubator during the next three days, after which recovery was rapid.

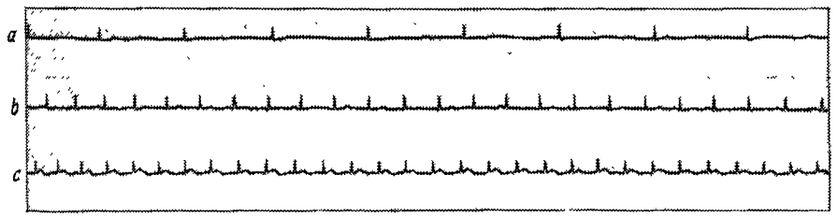


**Fig. 2—Selected sections of continuous E.C.G. from case 2: (*a*) at onset of compression aged 5 minutes, rate 45 per min.; (*b*) after 7 minutes' compression, rate 120 per min.; (*c*) after 16$^1/_3$ minutes' compression, rate 150 per min.**

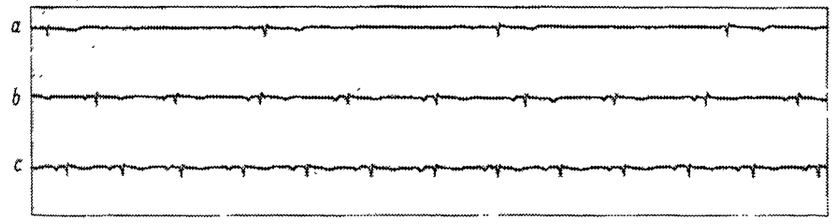


**Fig. 3—Selected sections of continuous E.C.G. from case 3: (*a*) at onset of compression aged 25 minutes, rate 20 per min.; (*b*) after 3 minutes' compression, rate 54 per min.; (*c*) after 7 minutes' compression, rate 65 per min.**

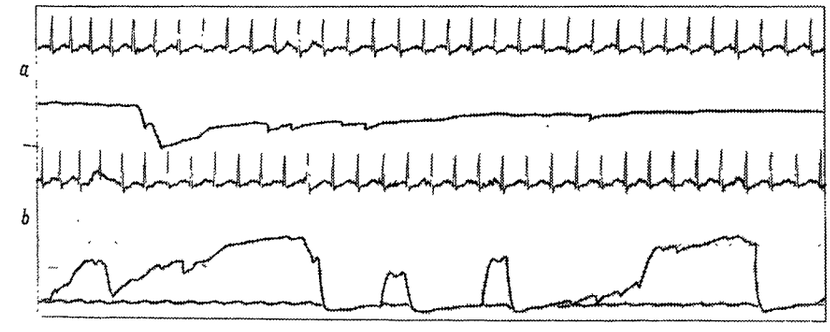


**Fig. 4—Selected sections of continuous E.C.G. and respiratory pattern from case 4: (*a*) after 30 seconds' compression, aged 7$^1/_2$ minutes, showing a gasp, heart-rate 168 per min.; (*b*) after 2$^1/_2$ minutes' compression showing established respirations, heart-rate 168 per min.**

**Case 3.**—The mother, aged 31, had had three normal pregnancies. Spontaneous labour occurred at twenty-nine weeks' gestation. A male infant, the first of twins, weight 0·78 kg., was spontaneously delivered by the vertex after an eight-hour labour. He was completely apnœic, cyanosed, and shocked. Apart from a solitary gasp at 4 minutes of age, there was no response to suction, oxygen by funnel, and intravenous nalorphine hydrobromide. Survival seemed impossible, but as there was still a heart-beat of 20 per min. (fig. 3*a*) after twenty-five minutes it was decided to place him in the pressure chamber. The Apgar score was 2. After three minutes' compression his colour had dramatically improved, and he had started to breathe in a jerky fashion. His heart-rate was 54 per min. (fig. 3*b*). After seven minutes, when the pressure was nearly 45 lb. per sq. in. the heart-rate was 65 per min. (fig. 3*c*). Decompression was started after fourteen minutes when respiration was almost regular. At the age of 2 hours the signs of R.D.S. appeared, and the infant died aged 10 hours and 20 minutes. Necropsy revealed immature lungs with both primary and resorption atelectasis, and hyaline membrane.

**Case 4.**—The mother, aged 28, had had five normal pregnancies. Severe antepartum hæmorrhage from anterior placenta prævia occurred at thirty-two weeks' gestation. A female infant, weight 2·22 kg., was delivered by lower segment cæsarean section. There was some fœtal blood-loss from incision of the placenta. The infant was deeply cyanosed and limp but there were no signs of severe hæmorrhage. A few ineffectual gasps were the only response to conservative measures of resuscitation. She was placed in the pressure chamber at the age of 7 minutes, when her heart-rate was 168 per min. and the Apgar score was 3. She took her first gasp in the chamber after thirty seconds (fig. 4*a*). After two and a half minutes, when the pressure was 20 lb. per sq. in., her colour was excellent and she was having fairly regular but uneven respirations (fig. 4*b*). Decompression was started after eight minutes. Unfortunately she developed severe R.D.S. She was treated with intravenous sodium bicarbonate, fructose, and blood-transfusion, but death occurred at the age of 51 hours and 45 minutes. Necropsy revealed extensive hyaline-membrane formation and gross bilateral intraventricular hæmorrhage.

### Discussion

Little is known about the stimuli which cause the normal infant to take his first breath (Burnard 1962). It is now thought that sensory stimuli (Barcroft 1946) are less important than the hypoxia which is always present at birth (Dawes 1958). An important factor may be the blood pH (Reardon et al. 1960). The previously held view that the fœtus suffers progressive

hypoxia with advancing pregnancy is now thought to be wrong (Dawes et al. 1960, Misrahy et al. 1962), and there is evidence to suggest that the most important stimulus to breathing is the sudden onset of mild asphyxia when the circulation in the umbilical cord is interrupted (Harned et al. 1961). On the other hand, there is little doubt that the major cause of apnœa neonatorum is excessive asphyxia due to such causes as antepartum hæmorrhage, premature separation of the placenta, and compression of the umbilical cord. The respiratory centre may also be damaged by traumatic intracranial hæmorrhage, but this is uncommon in modern obstetric practice.

Over thirty years ago Eastman (1932) pointed out that " there seems to be only one urgent indication in the treatment of asphyxia neonatorum, and that is to introduce oxygen into the circulating blood of the infant ". If this can be achieved the respiratory centre will start to function, always provided it has not already been irreversibly damaged by prolonged asphyxia or by trauma. In the apnœic infant who has not responded to simple methods of resuscitation, the most hopeful method of achieving this has been tracheal intubation and intermittent administration of oxygen. The rapid improvement in the infant's colour and heart-rate which may accompany this treatment even when the lungs are not inflated, must indicate that oxygen is diffusing through the mucous membrane of the respiratory tract.

In the present series we have obtained evidence that hyperbaric oxygen at pressures up to 4 atmospheres absolute (45 lb. per sq. in.) is an effective method of making oxygen quickly available to the anoxic tissues of the apnœic newborn infant. It has the advantage of speed, and the apparatus can be operated after only a short course of instruction. We have not observed any signs of oxygen poisoning over the short periods required for resuscitation, although there would obviously be dangers from long-continued exposure to hyperbaric oxygen above 2 atmospheres (15 lb. per sq. in.). Our results could probably be improved by earlier use of the pressure chamber than was possible in our limited experience. Apnœa neonatorum is not an emergency in which a controlled trial would be permissible, but it is our firm impression that hyperbaric oxygen is the most effective method of resuscitation yet devised for the severely asphyxiated newborn infant.

**Summary**

A trial of hyperbaric oxygen in the treatment of severe asphyxia neonatorum is described. In the apnœic newborn infant the hæmoglobin is grossly undersaturated, and the pulmonary alveoli are airless. Immersion of the infant in pure oxygen at 2–4 atmospheres of pressure produces a steep gradient of 1500–3000 mm. Hg between the environment and his plasma and tissue fluid, so that oxygen will diffuse into the circulating blood via the mucous membranes and the skin.

This attempt to force oxygen into the unsaturated blood was made in a ' Perspex ' pressure cylinder designed by the Vickers Group Research Establishment. 65 infants were treated. The Apgar score was recorded before compression, and in some infants continuous electrocardiographic and respiratory monitoring were achieved during compression. 35 infants (54%) recovered; 16 (25%) were successfully resuscitated but died more than six hours later from various causes; 14 (21%) failed to respond or lived for less than six hours.

It is concluded that hyperbaric oxygen therapy effectively makes oxygen available to the tissues of a severely anoxic newborn infant. Better results could probably have been achieved by more prompt use of the pressure chamber.

We wish to express our gratitude for their cooperation and support to our obstetric and nursing colleagues of the Glasgow Royal Maternity Hospital, and to the directors of the Vickers Group.

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# URINARY CORTICOSTEROID EXCRETION IN OBESE ADULTS

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OBESE children have a raised output of urinary steroids, and this is attributed to over-nutrition and functional hyperpituitarism (Cohen 1958). Corticosteroid excretion in obese adults has received scant attention, and the previously reported results are conflicting. Poisneck and DiRaimondo (1956) found a diminished output of 17-ketosteroids (17-K.S.) but increased urinary 17-ketogenic steroids (17-K.G.S.) in obese adults. Simkin (1961) observed a high excretion of urinary corticosteroids, including both 17-K.S. and 17-K.G.S., in his series of overweight adults. The difficulty in distinguishing clinically between simple obesity and Cushing's syndrome, and the occasional finding of an increased corticosteroid output in obesity, have prompted the present investigation into corticosteroid excretion in obese adults and the response to dietary restriction, adrenal suppression, and adrenal stimulation tests.

## Material and Methods

Obese adults were defined as being at least 28 lb. over the expected weight for age, height, and sex (Society of Actuaries 1959). 20 obese women were admitted to hospital; and on the first three consecutive days, while they were on a normal diet, three twenty-four hour urine collections were made and the average daily excretion was calculated. Concurrently, 20 women patients with a normal weight and normal dietary intake, and with no endocrine disorder, were admitted for comparison. They were chosen from non-endocrine medical cases including essential hypertension, disseminated sclerosis, gastric ulcer, and miscellaneous medical conditions. During the first three days, while these control patients were on normal diet, urines were collected, for comparison with the obese group. A larger series of 100 non-endocrine cases in women patients with a normal weight were investigated similarly to find out the range of steroid excretion with age.

The 17-K.S. and 17-K.G.S. were determined by the modified Gibson and Norymberski method (1954). The measurements of the urine 17-hydroxycorticosteroids (17-O.H.C.S.) and