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IATROGENIC DISEASE AND ANAESTHESIA*

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Knowledge of the action of anaesthetic drugs has increased in recent years, and with the advent of muscle relaxants and new techniques there remain few absolute contraindications to the use of anaesthesia. Some techniques are known to produce adverse effects in certain pathological conditions, such as spinal analgesia in the presence of disease of the central nervous system or the use of thiopentone in porphyria. However, more recently it has become apparent that many forms of routine medical treatment may affect the response to anaesthesia. This paper deals with some of these, and a more descriptive title would have been "The immediate and remote adverse influences of some routine forms of medical treatment on the response of patients to drugs used in anaesthesia and their effect on the mortality associated with the deliberate production of unconsciousness." The title is intended to refer to maladies and abnormal states which are unwittingly produced by physicians, other than anaesthetists, and for which the anaesthetic technique may well be blamed.

Sulphonamides

These were probably the first drugs that were thought to influence the effects of anaesthetics. Because of their sulphur, it was suggested in the early 1940's that their use precluded the administration of thiobarbiturates such as thiopentone, in case sulphaemoglobin-aemia might occur (Mallinson, 1941). They were said to intensify cyanosis and increase the toxicity of the thiobarbiturates, but this is no longer believed. Clinical experience has shown that thiopentone can safely be given to patients on sulphonamide therapy.

Hypotensive Drugs

Methonium Compounds.—In 1951 Davison warned anaesthetists to be aware of patients who were being treated with either pentamethonium or hexamethonium. At that time these compounds were being widely used as therapy for peptic ulceration, and should the ulcer perforate in such a patient he would be in a very grave pre-operative condition. The hypotensive effect of the methonium compound is more marked in the anaesthetized than in the conscious subject, and the hazard of anaesthesia in patients receiving these drugs is obvious. This is not merely a theoretical consideration, as the following reports will show.

Case 1.—Operation of transthoracic vagotomy on a patient who was on hexamethonium therapy. A severe fall in blood pressure occurred during induction of anaesthesia,

and became more marked when the patient was placed in the lateral position and the bridge on the operating table raised. The hypotension responded to infusion of L-noradrenaline, and the operation was carried out after a delay of almost one hour.

Case 2.—Perforated peptic ulcer in a patient on methonium therapy. Sudden death followed induction of anaesthesia with thiopentone and a muscle relaxant.

Case 3.—Proposed thoraco-lumbar sympathectomy on a patient who was on pentolinium ("ansolysen") therapy. A severe fall in blood pressure followed induction of anaesthesia and was accentuated by posturing the patient on the table. There was not a good response to intravenous methylamphetamine, and the operation was abandoned. The patient was very clouded mentally for several days after this incident and the possibility of cerebral thrombosis was considered.

In none of these cases was the anaesthetist aware of the methonium therapy. Had this been known the operation should have been postponed in Cases 1 and 3, and the administration of phenylephrine, methoxamine, or L-noradrenaline might have prevented the fatal outcome in Case 2. As is shown below, with other drugs, many of the hazards described can be prevented by letting the anaesthetist know what medical treatment is being carried out, and by anaesthetists being aware that some forms of routine medical treatment can modify the response to anaesthesia.

Mecamylamine.—Recent work in cats by Payne (1957) has shown that, after its administration, hexamethonium and trimetaphan camphorsulphonate produced neuromuscular block. There is a potential risk if this is eventually shown to apply to man. It is to be expected that patients receiving this drug are liable to the same changes in blood pressure during anaesthesia as patients on hexamethonium.

Rauwolfia.—This is not a ganglion-blocking drug, but causes hypotension by central depression of the vasomotor system. The lassitude and drowsiness which it causes suggest that it may potentiate narcotics. Coakley and his colleagues (1956) studied the circulatory changes during anaesthesia in 40 cases receiving rauwolfia therapy. Of these, 40% had a fall in blood pressure of more than 40 mm. Hg and a pulse rate below 60 a minute. The hypotension responded in a variable manner to vasopressors, but relieving the bradycardia with atropine or oxyphenonium ("antrenyl") was of help. In addition to the above, rauwolfia potentiates ganglion-blocking drugs and produces nasal congestion and excess salivation. There may be difficulty in maintaining a clear airway, and the risk of excessive bleeding after nasal intubation is increased. Rauwolfia has a

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slow onset of action, and its effects last for several weeks. Where possible the drug should be stopped two weeks before operation.

Veratrum Alkaloids.—The effect of these alkaloids on the cardiovascular system is complex and incompletely understood. Their main action is a reflex fall in blood pressure and a reflex fall in pulse rate, known as the von Bezold effect (Dawes *et al.*, 1951). This can be very confusing when it occurs in the anaesthetized subject.

Case 4.—A married woman aged 40. Hypertension for many years. B.P. 195/100. Treated for two weeks with "rauwiloid" and "veriloid" tablets. Operation was craniotomy and ligation of aneurysm carried out under hypothermia. Fig. 1 shows the course of anaesthesia. Note

FIG. 1.—Course of anaesthesia in Case 4. T=Thiopentone. P=Pethidine. C=Chlorpromazine. A=Oxyphenonium.

initial tachycardia with ether, accompanied by rise in blood pressure and same effect with trimetaphan. The hypotensive action of the trimetaphan was rapidly reversed by two 2-mg. doses of oxyphenonium.

It can be seen that all drugs currently used in the treatment of hypertension can affect the course of anaesthesia. It is essential that the anaesthetist knows well in advance of the operation when such drugs are being given, and on occasion it may be advisable to postpone surgery until their effects have worn off.

Cortisone, its Analogues, and Corticotrophin

It has been known for many years that patients with adrenocortical insufficiency tolerate poorly the stress of anaesthesia and surgery. In 1931 Rowntree and Snell stated that the risk of any surgical procedure in patients with Addison's disease was prohibitive, but modern substitution therapy has completely changed the picture. A review of reported anaesthetics to patients with Addison's disease (Dundee, 1957) reveals that out of 18 cases with no special pre-operative preparation 89% developed hypotension during or after anaesthesia and the mortality was 56%. In comparison, hypotension occurred in only 55% of 20 patients who received specific hormone therapy and there was no mortality associated with the anaesthesia.

This applies to all types of adrenal failure, including secondary hypoadrenocorticism caused by inhibition of the pituitary by cortisone or corticotrophin. Welbourne (1957) has called this primary pituitary failure, which is a more descriptive term. Cortisone inhibits the pituitary directly.

Corticotrophin stimulates the cortex to produce an excessive amount of cortisol, which in turn causes pituitary inhibition. After these substances have been withdrawn the pituitary-adrenal axis may take several months to recover normal function.

In adrenocortical insufficiency, patients react to the stress of anaesthesia and surgery by hypotension (out of proportion to the blood loss), respiratory depression, and delayed recovery. Different degrees of response are seen, depending on the severity of the condition and the stress. There are many published cases of peripheral circulatory failure developing during or after anaesthesia in patients who had cortisone therapy which was stopped within the three months before operation, or in patients in whom treatment was continued up to the day before operation, but where the all-important pre-operative dose was missed. One reported case got the pre-operative dose, but because of a delayed recovery from anaesthesia missed the evening dose and circulatory failure resulted. It is worth noting that in many incidences the operation was a minor one, not related to the condition for which the cortisone was given, and the period of anaesthesia was very brief. Procedures such as manipulation of a joint (Harnagel and Kramer, 1955), reduction of a dislocated shoulder, and dilatation and curettage (Dundee, 1957) have all been followed by profound hypotension in patients with primary pituitary failure.

Catastrophes from drug-induced adrenocortical failure are entirely preventable. In patients who are already receiving cortisone or corticotrophin an increased dosage should be given before operation. In patients who have stopped treatment within six months of surgery the problem is greater, especially in emergency cases, where it may not be known that such drugs had been used.

During the pre-operative examination all patients should be questioned regarding steroid therapy. One of the Chicago hospitals emphasizes the necessity for this, by having a special place on the anaesthetic record to note the pre-operative use of cortisone or corticotrophin (Karp, 1957). It must be remembered that prednisone and prednisolone are also powerful inhibitors of the pituitary, and their continued use may be followed by adrenocortical hypofunction. Surgeons will now feel happier about the cortisone therapy in view of the recent report by Popert and Davis (1958) that therapeutic doses do not interfere with wound healing.

There can be few better examples in medical practice of the saying "prevention is better than cure" than in the pre-operative management of adrenocortical insufficiency. This is illustrated by the following two cases.

Case 5.—A married woman aged 36 had a four-years history of diarrhoea. Motions varied significantly in frequency and con-

FIG. 2.—Course of anaesthesia in Case 5. T=Thiopentone. dTC=D-Tubocurarine chloride. M=Methoxamine. C=Cortisone. A=Atropine. N=Neostigmine. Doses in mg.

sistency with corticotrophin. General condition was good. Sigmoidoscopy showed purulent granular mucosa, but no ulceration. Barium enema showed whole colon to be spastic and devoid of haustrations; the terminal ileum was also affected. Operation was colectomy and ileo-rectal anastomosis. Pre-operative steroid therapy: 16-15 months, 20-30 units of corticotrophin daily; 14 months, 25 mg. of cortisone four times a day; 13-9 months, 20-30 units of corticotrophin daily; 8-3 months, 10-20 mg. of prednisolone daily; 2 months to 3 days, 20 units of corticotrophin daily. Pre-operative medication: promethazine, 25 mg., and atropine, 0.6 mg. Anaesthesia: thiopentone, D-tubocurarine, and N_2O-O_2 with mechanically controlled respiration. B.P. and pulse changes are shown in Fig. 2. The fall in blood pressure following induction was first attributed to the promethazine, and caused alarm only after it failed to respond to lowering the head of the table and intravenous methoxamine. Up to this stage the anaesthetist was not aware of the pre-operative steroid therapy. The response to cortisone and cortisol was dramatic, and thereafter the patient caused no further concern. Cortisone and corticotrophin were given in gradually decreasing doses for the first four to five days after operation.

Case 6.—A married woman aged 54 had had transverse colectomy performed for ulcerative colitis one year previously. At

FIG. 3.—Course of anaesthesia in Case 6. T=Thiopentone. dTC=D-Tubocurarine chloride. A=Atropine. N=Neostigmine.

that time there was an ulcerating area round the anus with a stricture of the rectum. The anal conditions had improved, although there was still some blood-stained purulent discharge per rectum and bleeding from the mucosa of the colostomy. Weight 91 lb. (41 kg.). Operation: abdomino-perineal resection of rectum and colon and terminal ileostomy. Pre-operative medication: cortisone, 100 mg.; corticotrophin 20 units; pethidine, 50 mg.; atropine, 0.6 mg. Anaesthesia was with the same technique as in Case 5 and there was no severe fall in blood pressure (Fig. 3). The only notable feature was marked resistance to D-tubocurarine, which may have been due to the liver dysfunction which was present, with an associated low pseudocholinesterase level. The post-operative period, during which corticotrophin and cortisone were continued, was uneventful.

In these cases the most marked fall in blood pressure occurred in the patient who had the less extensive operation and who was thought to be in the better pre-operative condition. In cases of adrenocortical hypofunction, hypotension responds rapidly to intravenous cortisol, but the usual attention should be paid to blood replacement and avoidance of hypoxia and hypercarbia.

Tranquillizers

The intensity of the search for ataraxia is shown by a recent review article which estimates that 50 million pounds' worth of tranquillizers were sold in the United States in

1956 (Gold and Stone, 1957). From the point of view of modifying response to anaesthesia the phenothiazine derivatives are the most important group, and the effects of chlorpromazine have been studied in detail. Other members of this series vary in their action in degree only and possess, to a greater or less extent, the same hazards as chlorpromazine. They include such drugs as promazine ("sparine"), promethazine ("phenegan"), acetypromazine ("notensil"), pectazine ("pacatal"), and prochlorperazine ("stemetil").

The effects of chlorpromazine vary with the duration of the treatment, dosage, route of administration, and the temporal relation of the last dose to the induction of anaesthesia. Long-term use continued up to the induction of anaesthesia can greatly prolong the duration of action of both narcotics and relaxants. Scanlon (1955) has described prolonged apnoea and delayed return of consciousness following thiopentone, gallamine, N_2O-O_2 and ether given for appendectomy in a patient who had been receiving 25 mg. of chlorpromazine three times daily for 14 months. Even a single pre-operative dose of chlorpromazine can greatly reduce the dose of thiopentone needed to produce sleep, and if large doses of the thiobarbiturate are given there will be some delay in return of consciousness. Surprisingly enough, in animals the long-term use of chlorpromazine, if discontinued for at least 24 hours before anaesthesia, can cause resistance to the thiobarbiturates. This is seen clinically to some extent in patients who have had chlorpromazine for the treatment of subarachnoid haemorrhage or head injuries. Any of the above effects may be modified if liver function has been depressed by the long-term use of the phenothiazines.

More important than its action in potentiating narcotics and relaxants are the cardiovascular effects of chlorpromazine. The drug itself can cause hypotension and tachycardia, both of which are increased by the head-up tilt and in the presence of hypovolaemia. Like the methonium compounds, it potentiates the hypotensive action of thiopentone. Because of its adrenolytic action, one would expect a severe fall in blood pressure in patients who have received chlorpromazine before ether anaesthesia. (Price (1957) has demonstrated an increase in circulating adrenaline during ether anaesthesia, and Brewster *et al.* (1953) have attributed its stimulating action on the cardiovascular system to reflex release of adrenaline. The increased cardiac output caused by ether anaesthesia in normal dogs is replaced by a marked decrease if measures such as adrenalectomy and chemical blockade are taken to prevent the sympathetic discharge caused by the ether.) This effect is not of great clinical importance, but it must be remembered that after chlorpromazine much smaller doses of ether are required. If concentrations comparable to those used in patients who have not had chlorpromazine are given, then severe hypotension may result.

Tachyphylaxis to the hypotensive effects of chlorpromazine follows its prolonged use. This is important when the drug is used as an adjuvant in the production of hypothermia by surface cooling. It is frequently found that under these circumstances normal doses are quite ineffective in producing peripheral vasodilatation. The long-term use of chlorpromazine also seems to induce resistance to ganglion-blocking drugs.

Animal experiments have shown that chlorpromazine modifies the response to vasopressor drugs (Bourgeois-Gavardin *et al.*, 1955). The action of the less potent sym-

Response to Vasopressors in Patients who Received Chlorpromazine

Drug	Dose	No. of Times Used	Good Response	Max. Rise of 20 mm. Systolic	No Response
L-noradrenaline	..	11	10 (91%)	1	0
Phenylephrine	2-10 mg.	10	9 (90%)	1	0
Methylamphetamine	8-60 mg.	9	1 (11%)	3	5
Methoxamine	5-20 mg.	13	3 (23%)	5	5

theticotonic drugs, such as ephedrine and methylamphetamine, is prevented completely, whereas the action of potent vasopressors is modified, but not inhibited completely, even by large doses of chlorpromazine. The importance of this in clinical practice is shown in the accompanying Table. The patients in this series all received at least 50 mg. of chlorpromazine before or during neurosurgical operations, and it can be seen that phenylephrine, in doses of 2-5 mg., is the most useful single-dose vasopressor under these circumstances.

Sedatives and Analgesics

The long-term use of these drugs is known to lead to tolerance to their desired therapeutic effects. This in turn causes cross-tolerance to the drugs used in anaesthesia. The intravenous thiobarbiturates are the best-known example, but this is probably because their actual dosage can be accurately measured and tolerance will be more easily detected. Increased dosage of curare-like relaxants is also required in patients who are tolerant to analgesics.

Unfortunately, resistance to thiopentone and similar drugs is more often seen in the type of patient to whom one does not wish to give large doses. It can be counteracted to some extent by increasing the pre-operative dose of morphine or pethidine, or by increasing the dose of relaxants used.

Another routine use of analgesics and sedatives which can cause trouble during anaesthesia is their subcutaneous administration to patients with peripheral circulatory failure. Because of their malabsorption more than one dose may be given, and when the vasodilatation due to the anaesthesia occurs or when adequate resuscitation has taken place these large doses will be released into the general circulation. There are many reported examples of respiratory depression at the end of operation which could be attributed to this cause. It is worth noting that both neostigmine and pyridostigmine can potentiate the effects of analgesics and possibly increase the degree of respiratory depression.

Drugs used in Treatment of Parkinsonism

It has been shown experimentally by Pulver (1955) that caramiphen ("parpanit," "panparnit") can potentiate barbiturates. There are no clinical reports of the significance of this action, and no explanation can be offered for the effect save that it may reduce muscle tone and that delayed recovery may be more apparent than real. However, a similar drug, benzhexol ("artane," "pipanol"), does seem to have some peculiar effect on the action of anaesthetics and possibly on muscle relaxants. Three cases of abnormal response to anaesthesia after its use have been brought to my attention, and the following report is typical of the sequence of events.

Case 7.—A 45-year-old man had been diagnosed as suffering from post-encephalitic Parkinsonism 19 years ago. For many years he had been treated with belladonna mixtures, but for the past four years had received benzhexol. The daily dosage at the time of operation was about 20 mg. Operation: orthopaedic emergency. Pre-operative medication: morphine, 10 mg., and atropine, 0.6 mg. Anaesthesia was induced with 350 mg. of 2.5% thiopentone and oral intubation carried out after 40 mg. of suxamethonium. As there was no return of spontaneous respiration the patient was inflated with nitrous oxide and oxygen and his general condition gave no cause for concern. He was still apnoeic 25 minutes later, when the operation was completed. After one hour he appeared to be remarkably light and objected to pulling on the tube, although he made no attempt to breathe. Extubation and reintubation was of no avail. In view of the muscle tone which was present it did not seem as if this was a case of suxamethonium apnoea, and bemegride was given without response. Nalorphine likewise produced no improvement. The eyelash reflex returned after 100 minutes and he was breathing periodically 50 minutes later. Three and a half hours later he opened his eyes when shouted at. His condition was not normal for a further two to three hours. He would sit up in bed suddenly and stare wildly, then lapse back again. The post-operative behaviour somewhat resembled the oculogyric crises of encephalitis lethargica or post-encephalitic tic.

One case of benzhexol-barbiturate poisoning showed no response to bemegride-amiphenazole and remained apnoeic for four hours and unconscious for three days. This is suggestive of some synergism between the barbiturates and anti-Parkinsonism drugs.

Ethopropazine hydrochloride ("lysivane"), a phenothiazine derivative, also used in the treatment of Parkinsonism, can be incriminated as a possible cause of prolonged apnoea and delayed recovery in another case. The potentiation in this patient may have been due to the same causes as those responsible for the prolongation of barbiturate narcosis by chlorpromazine (Dundee and Scott, 1958).

No explanation can at present be offered for the effect of anti-Parkinsonism drugs on the response to anaesthesia. It is not even certain whether the drugs themselves were to blame, and certain cases of Parkinsonism may themselves react abnormally to anaesthesia. However, this is unlikely, as there are no reported cases in the literature.

Oral Fluids

Out of 589 fatalities associated with anaesthesia, reported by Edwards *et al.* (1956), the largest single cause of death was regurgitation and vomiting followed by aspiration. Of the 110 deaths from this cause, 70% occurred in surgical emergencies, but two groups come within the scope of the present discussion.

Diabetics.—There were six deaths in cases where oral glucose solution was given pre-operatively, as is customary, and subsequent regurgitation or vomiting of fluid brought about the death of the patient. On five of these the operation to be performed was quite trivial. Water passes rapidly into the duodenum, but hypertonic glucose solution prolongs the emptying time of the stomach. In some animals the solution has to be diluted in the stomach until it is isotonic before it passes into the duodenum. Morton and Wylie (1951) suggest this as a possible explanation for these unfortunate occurrences. It is recommended that the practice of giving glucose solution by mouth be discontinued. If pre-operative glucose is essential it should always be given by the intravenous route.

Obstetrics.—Apart from the report already referred to, in which 15 deaths occurred from vomiting or regurgitation during delivery, there have been many publications drawing attention to this hazard, notably those of Parker (1954, 1956). The inhalation of liquid material can cause an asthmatic type of attack, with bronchospasm, pulmonary oedema, and cardiac failure. Death usually occurs within 36 hours of delivery. Much has been written about the prevention of these deaths during forceps delivery or caesarean section. The greater use of local analgesia, abandonment of the lithotomy position, and the routine passage of widebore stomach tubes before induction of anaesthesia have all been recommended. The answer probably lies in appreciating that absorption from the intestine is disturbed during parturition. Hawkins and Nixon (1957) have confirmed that this occurs during labour lasting more than a few hours. The *Lancet* (1957) admirably summarizes the situation: "There is little point in forcing solid food and extra fluids by mouth once labour has lasted more than 24 hours, for the material will often not be absorbed and merely encourage vomiting, thus increasing the risk of inhalation of stomach contents if anaesthesia has to be induced."

Radiation Therapy

Wilson (1955) found that animals exposed to x-ray therapy of the whole body showed an exceptionally poor tolerance to cyclopropane, but not to ether, ethylene, nitrous oxide, or thiopentone. Death resulted from respiratory failure occurring at an abnormally light plane of anaesthesia.

One reported case (Foster, 1956a) suggests that these findings may be applicable to man. Following deep x-ray therapy to a carcinoma of the mouth five weeks before operation, it proved impossible to maintain the patient on

cyclopropane because of the extreme and unusual sensitivity that he showed. A gas flow of 200 ml. a minute produced respiratory arrest for approximately half an hour, and the patient responded to painful stimuli before respirations became properly re-established.

Several unsuccessful attempts, with similar results, were made to maintain anaesthesia with cyclopropane, and the operation was eventually completed with nitrous oxide, oxygen, and ether and pethidine. During these periods of respiratory depression the pulse rate and blood pressure were relatively unaffected, although it was thought that temporary cardiac arrest had occurred earlier following endotracheal intubation. At the second-stage operation, one month later, cyclopropane was avoided and thiopentone, nitrous oxide, oxygen, pethidine, and alphaprodine ("nisentil") were given without any unusual effects.

Foster (1956a), from a review of the literature, suggests that irradiation around the head in appropriate doses may increase the permeability of intracranial vessels, and drugs which normally penetrate the blood-brain barrier may do so to a greater degree. The peculiar pattern of neuronal radiation damage seen suggests that excessive vagal tone may increase the hazards of intubation with cyclopropane, that consciousness may be more easily depressed, and that disturbances of temperature regulation may be encountered.

This case not only focuses attention on the potential hazards of deep x-ray therapy, but shows problems which may have to be faced following an atomic explosion. Whether penetration of relaxants across the blood-brain barrier occurs under these circumstances is not known, but the possibility should be kept in mind, especially if prolonged curarization is encountered (Foster, 1956b).

"Pitocin"

The intravenous use of the oxytocic principles of the pituitary gland is now an established practice in obstetrics. There are many reports of the dangers of administration where "pituintrin" and "pitressin" have been used. The pressor principles cause cardiac irregularities, hypotension, coronary constriction, and bronchospasm.

"Pitocin" is relatively free of vasopressin (but not completely so), and one would expect it to be less dangerous than the more impure preparations. However, Lesser and Eason (1954) have reported a death from the use of pitocin during emergence from light cyclopropane anaesthesia. They attributed this to the administration of vasopressin (although in a very dilute form) to a patient with impaired coronary circulation who was in a state of heightened vagal reflex activity associated with recovery from cyclopropane. It is important to note that the patient had recovered sufficiently to make purposeful movements of the arms, and that Parsloe *et al.* (1950) had previously shown that deep anaesthesia protects against arrhythmias and coronary constriction. It should also be mentioned that cardiac arrest occurred about one minute after starting the pitocin infusion and that necropsy revealed some degree of coronary artery disease.

Others

With some other drugs the relationship between the patient's condition and non-anaesthetic drugs is less obvious than with those already described. They should, however, be borne in mind.

Citrate Intoxication.—An increase in venous pressure with gradual onset of cardiac failure during massive transfusions may be due to this. It should be suspected if there is a poor response to apparently adequate blood transfusion, especially in patients with liver disease, during hypothermia, or where the hepatic circulation has been temporarily occluded. A death was reported from transfusion of 750 ml. of blood in the course of five minutes to a 4-months-old girl, and analysis showed that circulating blood had a citrate level equal to that of donor blood (*Curr. Res. Anesth.*, 1957). Bunker *et al.* (1955) recommend raising the level of ionized calcium by giving calcium chloride, in a 1%

solution, 1 g. per 150 lb. (84 kg.) in 10–15 minutes as a priming dose, then 1 g. per hour as a continuous infusion. Firt and Hejhal (1957) recommend the concomitant use of procaine, and mention the important practical point that the calcium should never be given in the same transfusion bottle as the blood.

Obstetrics.—Failure of the baby to breathe after delivery may be attributed to the anaesthetic, especially if thiopentone is given, without any reference to previous analgesics. Roberts *et al.* (1957) have demonstrated the depressant effects of pethidine on foetal respiration, which may be very pronounced if the drug has been given to the mother less than three and a half hours before delivery.

Hypoxia.—Bedford (1955) has described the adverse effects of anaesthesia on old people. It does not seem to be realized that harm can be done to these patients by routine prescribing of large doses of morphine or other analgesics before or immediately after operation. Dementia is as likely to be due to hypoxia from such drugs as to any incident during the anaesthesia.

Summary and Conclusions

This paper draws attention to the increasing use in medicine over the past few years of drugs which influence the response of patients to anaesthesia. This side-action cannot usually be predicted by pharmacologists, and often it was detected only by chance when the preparation in question had been in clinical use for several years. In all the instances reported above the effect was to engender in patients an increase in toxicity of one or other of the effects of general anaesthetics.

Therapeutic agents whose main effect is to decrease vascular tone, such as the ganglion-blocking drugs or chlorpromazine, if given before anaesthesia, increase the hypotensive action of the narcotics, and severe and even fatal collapse may follow what are considered to be normal doses of anaesthetic drugs. This applies particularly to the intravenous barbiturate anaesthesia, where it is difficult, even in normal subjects, to predict the degree of hypotension that will follow injection and to adjust the dose so as to minimize this action. Care must also be taken in anaesthetizing patients who are receiving other hypotensive agents such as the rauwolfia or veratrum alkaloids or mecamylamine.

Clinical and experimental evidence shows that the phenothiazine derivatives prolong the narcotic action of anaesthetics. This also seems to apply to the non-phenothiazine preparations which are used for the control of tremor in Parkinsonism, and possibly may be a side-effect of all the tranquillizers.

A dangerous degree of respiratory depression can result from the combination of analgesic drugs and the intravenous barbiturates. A similar result can occur when cyclopropane is administered to patients who have had deep x-ray therapy to the head and neck.

Induced adrenocortical insufficiency, following the prolonged use of cortisone, its analogues, and corticotrophin, makes patients sensitive to the stress of surgery and anaesthesia. Prolonged severe hypotension, respiratory depression, and delayed recovery may follow surgical operations in such patients. These undue effects respond rapidly to intravenous cortisol, but prevention by increased pre-operative dosage of cortisone and corticotrophin is preferable. Increasing use of the steroids is focusing attention on this hazard, and especially so in minor cases, where one does not normally associate any risk with anaesthesia. It must also be stressed that steroid-induced primary pituitary failure may persist for several months after stopping the drugs.

The hazards of inducing anaesthesia in patients with a full stomach are now widely appreciated, and for this reason the pre-operative preparation of diabetic subjects with oral glucose is deprecated. Other problems which anaesthetists may encounter are the incompatibility of pitocin with light cyclopropane anaesthesia and the possibility of citrate intoxication as a differential diagnosis for cardiovascular collapse after massive transfusion of stored blood.

In very few of the cases reported did the anaesthetist know of the use of various drugs before operation, or associate hypotension or prolonged unconsciousness with any form of routine medical treatment. It is hoped that this publication will focus the attention of all medical practitioners on the fact that during anaesthesia unexpected adverse effects may be produced by drugs which do not appear to have any side-effects in the conscious subject. It is to be expected that many additions to the list of drugs discussed above will be noted in the future.

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At a meeting of the South-eastern Branch of the B.M.A. on June 23, 1858, Dr. H. R. SILVESTER gave the first account of his method of artificial respiration. After considering other methods already in use, including that introduced by Marshall Hall two years previously, he described his own, in which, with the patient in the dorsal position, the arms are pulled over the head to enlarge the capacity of the chest and induce inspiration, and are then returned to the sides to diminish the cavity of the thorax and produce forcible expiration, the whole process being repeated at the rate of 15 times a minute. Silvester's account was published in the *British Medical Journal* on July 17, 1858, at p. 576.

THE RISK TAKEN IN DRIVING UNDER THE INFLUENCE OF ALCOHOL

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Alcohol as a cause of accidents on the road has been widely studied. The investigations that have been carried out, valuable as they are, suffer, however, from a serious limitation. They have usually determined the effect of alcohol on the driver by measuring changes in his reaction time and in his skills, such as steering and braking (Smith, 1945; *Handbook*, 1952; Piret, 1952; Thompson, 1956). Large quantities of alcohol do, of course, produce deterioration in skill and reaction time, but the conclusion has too hastily been drawn that because no changes have been recorded after small quantities road safety is unaffected. This conclusion is not justified, for all that can be inferred from earlier inquiries is that these skills and reaction times are or are not affected. It cannot, for example, be inferred that a driver is not a menace on the road because his reaction times are unaffected or because a test of skill revealed no impairment. The decisive feature is not the driver's skill in itself but in relation to what he believes he could do and what he would in fact undertake. Thus the negative outcome of these studies may signify only that the methods of measurement were inadequate, not that the alcohol was without effect on the safety of the individual's driving.

Our aim, therefore, is to assess the effects of alcohol on the more complex psychological processes and performances involved in risks which drivers take and in hazards which they incur. By "risk-taking" we mean embarking on a task without being certain of success. There can be various degrees of certainty of success and hence varying degrees of risk-taking. By "incurring hazard" we mean embarking on a task in which the performer will not invariably succeed. Thus risk is measured by estimates of success before the task is attempted, whilst hazard is measured by the proportion of successes in actual performance (Cohen and Hansel, 1956). In our previous studies (Cohen, Dearnaley, and Hansel, 1955, 1956a) of risks and hazards taken by inexperienced and experienced drivers we found that, on the average, experienced drivers tended to (1) take less risk, (2) incur less hazard, (3) vary less in their driving behaviour, (4) be more realistic in judging their driving ability, and (5) be prepared to drive only when they felt secure and were in fact safe; on the other hand, an instructor with long experience drove without risk or hazard. That is to say, he never attempted a task unless he was sure he would succeed, and he never failed in any task which he undertook.

These results suggested that a comparison of drivers who had imbibed various quantities of alcohol with drivers free of alcohol might reveal similar differences. The present inquiry was designed to measure the influence of alcohol on those drivers who might be expected to show its effects least—namely, bus drivers of long