IRRATIONAL POLYPHARMACY IN ANAESTHESIA*

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The present age is an age of anxiety and tension that gives rise to psychosomatic disturbances with widespread manifestations of depression; hypertension; coronary disease; gastric, duodenal and intestinal ulceration; and hormonal disturbances.

In our contemporary world vast numbers of the population, because of the tempo and pressure of modern living, use some form of sedative, tranquillizer or antidepressant drug. To these must be added antihypertensives, anticoagulants, antihistaminics, drug combinations containing amphetamine or its derivatives, and steroids.

Drugs cannot change the circumstances that are making life almost unbearable for so many people today and they cannot cure emotional illness, but they can reduce tension and help to restore morale. The whole medical profession has grown to realize that the wise and safe use of sedatives and antidepressives is one of the necessities of modern life.

This paper is presented to draw attention to the dangers to anaesthetized patients who have previously been subjected to one or more of the many forms of routine medical treatment or other forms of therapy, and to the dangers from drugs and combinations of drugs employed by the anaesthetist for pre-operative medication, during the course of anaesthesia, and in the postoperative phase.

Iatrogenic maladies and abnormal states, produced by physicians and surgeons and other therapists through various forms of treatment, have made it imperative to re-assess the action of commonly used anaesthetic agents. Psyche and soma are altered to such an extent by modern treatment that the physiology of anaesthesia will have to be rewritten. These abnormal clinical and physio-pharmacological responses occur in anaesthetized patients who have had those induced maladies superimposed upon already existing pathological conditions.

Great care will have to be exercised in accepting findings from trials of new anaesthetic agents on animals and humans who have not been subjected to modern drugs which can cause iatrogenic disease. Anaesthetic drug trials on animals are undoubtedly an important aid in carrying out investigations, but it does not necessarily follow that findings in animals will be identical and capable of duplication in the anaesthetized human patients — especially in cases of patients previously exposed to therapy with dangerous potentialities.

Whenever a new anaesthetic agent is developed, the usual procedure is to study its pharmacological action in detail in animals, in biological laboratories. But animals subjected to these agents are usually free of organic or iatrogenic disease and, of course, have central nervous systems which are not identical with those of man. This method of investigation is certainly most valuable, but it must again be emphasized that it is fallacious to apply results so obtained without reservation to man, and take it for granted that identical phenomena and reactions will be duplicated in him.

When encouraging results are obtained from pharmacological investigations in animals, these are usually followed-up by clinical and pharmacological studies in man. But here, too, as has been pointed out in the case of animals, there are certain difficulties. There is, firstly, the unpredictable individual factor in man. Secondly there is the presence of organic disease which affects his physical and psychical state. Thirdly there is today the possibility of having had superimposed one or more of the so-called diseases of medical progress which can further disturb the already disturbed psyche and soma.

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TABLE I. IATROGENIC DISEASES (SYNDROMES) — THEIR CAUSES AND ANAESTHETIC HAZARDS*

Diseases (syndromes)	*Causes*	*Anaesthetic hazards*
	General syndromes	
Tracheo-bronchial infections	Prolonged antibiotic therapy resulting in resistant staphylococcal infection	Tracheal intubation might aggravate this condition. Unsterilized endotracheal tubes may introduce other pathogens
Prolonged, profound respiratory depression	Neomycin and streptomycin used intra-abdominally[9]	Effect of prolonged curarization may be produced
Ano-rectal syndrome causing burning and melaena	Broad-spectrum antibiotics	The use of the rectal route for administration of anaesthetics or premedication may be blamed for the production of these syndromes
Neurologic disturbances (toxic mechanism results in paraesthesias) of hands, tongue and circumoral areas — may last a long time	Streptomycin and polymyxin	The anaesthetist may be held responsible for malposition of arms on the operating table — the use of airways, gags and packs may also be held to be the cause of these disturbances
Nephrotoxic effects	Streptomycin and neomycin	Kidney function is of vital concern to the anaesthetist. Every form of anaesthesia greatly reduces renal function — in fact operations requiring anaesthesia are of no avail in the presence of serious renal disease. Nephrotoxic effects from antibiotics must be taken into account
Penicillin reactions	Penicillin	Many anaesthetists are aware of dangerous reactions — sometimes fatal. Anaphylaxis and its danger must constantly be borne in mind. History is important before administration
	Cardiovascular effects and arrythmias	
Paroxysmal ventricular tachycardia	Digitalis Quinidine	Sixty per cent of all patients under general anaesthesia show arrhythmias by electrocardiography. These may become serious when superimposed upon arrhythmias of various types induced by drugs used in treatment
Paroxysmal tachycardia Ventricular fibrillation Cardiac arrest	Procainamide	
Premature contractions Central depression of vasomotor system	Rauwolfia alkaloids	Rauwolfia may drop pressure by 40 mm. or more and may produce nasal congestion; excessive bleeding may result from nasal intubation
Profound hypotension and arrhythmias	Chlorpromazine (tranquillizers)	
Arrhythmias	Thyroid drugs	
Angina pectoris Hypotension Myocardial infarction Cerebral vascular insufficiency	Anti-hypertensive drugs	Anti-hypertensive drugs should be stopped two weeks before operation. Surgery may even have to be postponed. Anti-hypertensive therapy represents a real hazard when associated with anaesthesia
Haemorrhagic infiltration of skin, subcutaneous tissues — necrosis, ulceration	Coumarin preparations	The coumarin preparations may be responsible for major bleeding during and after operations. Severe bleeding has taken place after dental extractions
	Haematological effects	
Anti-granulocytic reactors	Phenylhydrazine, dinitrophenol, sulphonamides, antithyroid drugs (thiouracil), antibiotics (streptomycin), tranquillizers ('sparine', 'pacatal'), barbiturates	Interference with immunological processes
Anti-erythrocyte reactors	Sulphonamides, chloramphenicol, phenacetin, tranquillizers, (meprobamate)	One of the main obligations of the anaesthetist is to ensure adequate supply of oxygen to tissues of patients under anaesthesia. Under these circumstances there is real hazard
Anti-platelet reactors	Sedormid, sulphonamides, digoxin, etc.	Such a state of affairs is also hazardous for the anaesthetist

Diseases (syndromes)	*Causes*	*Anaesthetic hazards*
	Hepatic and gastro-intestinal diseases	
Jaundice from intra-hepatic obstruction Hepatic coma	Chlorpromazine chlorothiazide 'diamox', etc.	Liver-function derangements are common in anaesthesia, but most anaesthetic agents, judiciously administered, produce minimal damage. In the presence of iatrogenic disease this may not be the case
	Hormone-induced diseases	
Adrenal exhaustion syndrome Hypercorticism states and steroid withdrawal syndrome Thrombo-embolic complications	Cortisone Prednisone } pituitary Prednisolone } inhibitors causing adrenal hypo-function	Steroid therapy induces adreno-cortical insufficiency, and patients so treated die of adrenal exhaustion during periods of stress such as surgery, anaesthesia, childbirth, accidents, etc. Hypotension out of all proportion to blood loss, respiratory depression, and delayed recovery may be the results of lack of care in handling such patients *N.B.* History must be elicited adequately before the operation; postoperative steroid therapy must be instituted in such cases
	Metabolic diseases	
Low-sodium syndromes True iatrogenic plasma-sodium depletion	Powerful diuretics Low-sodium diets	Muscular cramps, nausea, drowsiness, and diminution in renal flow may result in uraemia. This is again an added anaesthetic hazard
	Syndromes of therapy	
Anaemias of surgery (*a*) Normocytic hypochromic anaemia (*b*) Megaloblastic anaemia	Gastric resection	All anaemias are a hazard for the anaesthetist. Oxygen-carrying capacity is diminished under these circumstances
Radiation-therapy syndrome (poor tolerance and sensitivity of patients)	Radiation therapy	Patients exposed to radiation are very sensitive to cyclopropane anaesthesia and show marked respiratory depression at light levels of anaesthesia
Citrate intoxication	Massive transfusions of citrated blood	Citrate intoxication manifested by a marked increase of venous pressure and cardiovascular failure

* The above-mentioned list of iatrogenic diseases is by no means complete, but it serves to indicate how much greater responsibility the present-day anaesthetist has in carrying out his duties. It must be pointed out that although much of modern drug therapy is well-conceived and necessary, a great deal of ignorant, irrational, irresponsible, dangerous, and reckless polypharmacy is nevertheless practised.

TABLE II. COMBINATIONS OF DRUGS USED IN 11 CASES SELECTED AT RANDOM

Operation	*Premedication*		*Duration of operation*	*Anaesthetic agents and drugs employed in the operating theatre*
Case 1 Dilatation and curettage	'Omnopon', gr. $\frac{1}{3}$ Scopolamine, gr. 1/150		10 min.	'Sodium pentothal' N_2O/O_2 'Trilene' Fluothane
Case 2 Laparotomy	'Phenergan', 50 mg. 'Carbrital', gr. 6 Omnopon, gr. $\frac{1}{3}$ Scopolamine, gr. 1/150	Night before	150 min.	Sodium pentothal 'Scoline' N_2O/O_2 'Leostesin' (1%), 30 ml. Fluothane, 2¼ hrs. 'Methedrine', 1 ampoule
Case 3 Gastrectomy	Omnopon, gr. $\frac{1}{3}$ Scopolamine, gr. 1/150		215 min.	Sodium pentothal Tubarine, 60 mg. N_2O/O_2 Fluothane, 3 hrs. Atropine, gr. 1/100 'Prostigmin', 4 ampoules of 0·5 mg. each
Case 4 Bilateral hernia	Omnopon, gr. $\frac{1}{3}$ Scopolamine, gr. 1/150 Phenergan, 50 mg. Carbrital, gr. 3	*Nocte*	45 min.	Sodium pentothal Scoline N_2O/O_2 'Flaxedil' 160 mg. Atropine (2 ampoules of gr. 1/100) Prostigmin, 2 ampoules of 0·5 mg. each Fluothane ? %

Operation	*Premedication*	*Duration of operation*	*Anaesthetic agents and drugs employed in the operating theatre*
Case 5 Appendicectomy	Omnopon, gr. ⅓ Scopolamine, gr. 1/150	30 min.	Sodium pentothal N_2O/O_2 Scoline Flaxedil Fluothane
Case 6 Dental extraction	Omnopon, gr. ⅓ Scopolamine, gr. 1/150	30 min.	Sodium pentothal Flaxedil, 80 mg. Fluothane N_2O/O_2 Atropine, gr. 1/100 Prostigmin, 0·5 mg.
Case 7 Laparotomy—appendicectomy	Omnopon, gr. ⅓ Scopolamine, gr. 1/150	55 min.	Sodium pentothal Tubarine, 15 mg. Flaxedil, 80 mg. Scoline Fluothane Atropine, gr. 1/100 Prostigmin, 2 ampoules of 0·5 mg. each 'Lethidrone', 2 ampoules
Case 8 Haemorrhoidectomy	Phenergan, 50 mg. Carbrital, 6 gr. } *Nocte* Omnopon, gr. ½ Scopolamine, gr. 1/150	35 min.	Sodium pentothal N_2O/O_2 Fluothane 'Leostesin' (caudal) Adrenaline
Case 9 Cystoscopy, fulguration	Omnopon, gr. ⅓ Scopolamine, gr. 1/150	55 min.	Sodium pentothal Fluothane N_2O/O_2 Flaxedil, ? mg. 'Valoid', 50 mg.
Case 10 Prostatectomy	Omnopon, gr. ⅓ Scopolamine, gr. 1/150	120 min.	Sodium pentothal Scoline Flaxedil Fluothane N_2O/O_2 Methedrine, 2 ampoules Atropine Prostigmin
Case 11 Rib resection and empyema drainage	Not stated	?	Sodium pentothal, 200 mg. Tubo-curarine chloride, 30 mg. N_2O/O_2, 50 : 50 Halothane, 1% External cardiac massage 'Wyamine'

This widespread and often injudicious use of potentially harmful drugs — irrational polypharmacy as I have called it — makes the study of induced diseases of medical progress (iatrogenic diseases) one of continuing and dynamic interest to all anaesthetists and to all practitioners.

I have mentioned the high incidence of emotional illness in the population. The class of drugs to which has been given the name tranquillizers, sedatives, ataractics, central sympathetic suppressants, and calming or peace pills and potions, are used universally.

1. There are at least 100 brands of these drugs, each with a different trade name. It was estimated 5 years ago (1956) that £50 million worth of tranquillizers were sold in one year in the USA.[1-3] The phenothiazine derivatives, of which chlorpromazine is the most commonly used, have a wide range of pharmacological action. A list of actions of chlorpromazine is most revealing, and many are of profound importance to the anaesthetist. Chlorpromazine has adrenergic-blocking, local anaesthetic, parasympatholytic, antipyretic, weak ganglion-blocking, antihistaminic, and quinidine-like actions. The drug is capable of producing allergy leading to dermatitis, jaundice, and agranulocytosis. On the central nervous system, low doses abolish parkinsonian tremor and large doses induce parkinsonism. It abolishes spasticity and tetany. It potentiates barbiturates powerfully. It abolishes conditioned reflexes, but not in-

born reflexes. Chlorpromazine quietens aggressive rhesus monkeys and prevents hyperthyroidism. Arousal reactions induced by stimulating the frontal hypothalamus or ascending reticular formation are suppressed; the EEG studies are compatible with this being the principal site of action. It is also a powerful anti-emetic.

2. Chlorpromazine effects have been studied in detail from the aspect of modifying the responses of patients to anaesthesia. Long-term treatment can prolong duration of narcotics and relaxants. There have been reports of prolonged apnoea, delayed return to consciousness, and also a marked potentiation of barbiturates.[4] The commonest cardiovascular effects after the use of chlorpromazine are hypotension and tachycardia.

The widespread actions of the tranquillizers, as indicated above, and those of many other drugs and their common usage in vast numbers of the population, indicate how imperative it is for the anaesthetist to obtain a proper medical history from the patient. Has he taken or had prescribed any of these drugs for long or short intervals?

The approach to these patients for anaesthesia must be cautious. It is necessary to take the greatest care in administering tranquillizers in the pre-operative and post-operative phases, and during operative procedures. It is obvious that whatever anaesthesia is superimposed, due consideration must be given to the physiological aberrations which may have been induced previously and which, although not obvious in the conscious patient, can have disastrous effects in the anaesthetized (unconscious) patient.

It would be profitable at this juncture to list a number of iatrogenic diseases and their causes. Knowledge of these is vital to the anaesthetist (Table I).

Special anaesthetic care must be given to these patients because there may be serious consequences with possible mortality for which the anaesthetist might be held responsible, although in fact these may arise entirely from previously induced diseases.

Pre-anaesthetic Medication

Attention must now be directed to the dangers of polypharmacy in premedication of patients. These dangers arise not only because of superimposed iatrogenic disease, but from prescription of drugs by the anaesthetist which might profoundly influence the course of anaesthesia and the emergence from unconsciousness. Pre-anaesthetic medication must be planned with the entire picture of the patient, the operation, and anaesthesia in mind.

Few patients are so stoical that they do not need some mental block before operation. Enough has been said about tranquillizers in general to bar their use for premedication. Surely the best tranquillizer of all is the anaesthetist himself. In his pre-operative visits he can, by his art (this is still of paramount importance in the practice of anaesthesia), reassure and instil confidence into his patient without inducing morbidity. What can be less harmful than a suitable dose of scopolamine? What better amnesic is there? Furthermore, it is well known that many undesirable phenomena from reflex irritability are prevented by judicious atropinization; and sensory (pain) block may be assisted or enhanced by the administration of a preparation of the total alkaloids of opium now obtainable with a component which selectively antagonizes the respiratory depression caused by morphine. These simple innocuous measures should be sufficient for adequate and safe pre-operative medication.

Unfortunately the practice of prescribing combinations of drugs is now the vogue. There are dangers in using many of these drugs even singly, and in combinations it must be quite impossible to ascertain or assess the benefits or detriments of any one drug in the combination.

A perusal of patients' treatment charts (Table II) reveals that many patients receive a tranquillizer, e.g. chlorpromazine, 50 mg., combined with a large dose of a barbiturate, the night before operation. On the morning of the operation, one hour or an hour and a half before operation, they receive 'omnopon', 1/3 gr., with scopolamine, 1/150 gr. It has been proved[5] that sympatheticotonic drug action (by use of vasopressors) may be completely annulled when even small doses of chlorpromazine have been administered pre-operatively or during operation. Moreover, the tranquillizers have a powerful potentiating action on barbiturates. This exemplifies the irrational and potentially dangerous polypharmacy in the pre-operative phase.

Polypharmacy During Anaesthesia

New anaesthetic agents and new techniques are constantly being introduced. They come in rapid succession and even simultaneously, and claims which are often extravagant are made for these new agents with reference to their safety and potency. Each agent is said to have advantages over others and even over those which have stood the test of time.

Production of the state of anaesthesia is a complex process, and the exact mode of action of anaesthetic agents in order to produce anaesthesia is still undetermined. The ideal agent has yet to be elaborated. Physiological trespass occurs with every administration, and, although much has been done to reduce mortality, morbidity remains incalculable and may persist for a considerable period — sometimes for a life-time! Cardiac arrest has become a frequent occurrence. The anaesthetist is a clinical physiologist, but it becomes impossible for him to gauge accurately the clinical status of the anaesthetized patient when a multitude of anaesthetic agents are used simultaneously. The frequency of this practice can readily be seen by referring to operating theatre registers. These reveal a kind of polypharmacy which is responsible for serious morbidity and even deaths. It is not surprising that cardiac arrest is on the increase.

The human body was never designed for such assault, and much less is it able to tolerate such treatment when there is some pathological process present.

There seems to be a widespread belief that each ingredient in this potpourri has a selective site of action on specific organs or systems and leaves others unscathed. No account is taken of, nor is it known, what effects individual agents have on each other in combination, or what happens to the body as a whole when it is subjected to such combinations.

The position, of course, becomes even more complicated when there is not only organic disease present, but also superimposed iatrogenic disease.

In view of this it has, for instance, become necessary to develop a special technique of pre-anaesthetic preparation and anaesthetic management for patients who have been treated for long periods by anti-hypertensive drugs.[6] The method is based on the pharmacological action and the subsequent haemodynamic effect of the various anti-hypertensive agents. Not only are new multiple anaesthetic agents used, but the anaesthetist is persuaded to use drugs which derange even further, and even abolish, many of the vital compensatory mechanisms of the body. I refer here to the widespread use of the hypotensive ganglion-blocking drugs, which are so freely used in the operating theatres. They are used mostly to promote surgical facility, very often in trivial surgical procedures and very often without the anaesthetist being fully aware of the possible dangers and morbidity to which he exposes his patient. The patient for surgery who has had previous therapy which influences the course of anaesthesia; for whom multi-ingredient type of pre-medication has been prescribed; and to whom a combination of anaesthetic agents is administered, and then has superimposed a drug to induce purposeful hypotension, has certainly been exposed to grave danger. This is dangerous irrational polypharmacy and cannot be condemned too strongly. The information in Table I exemplifies what is very common practice among anaesthetists in certain parts of this country. It may be even worse elsewhere.

It will be seen from this random selection of 10 cases (Table II) (the eleventh was published in a recent issue of the *Journal*) that 'methedrine' was administered to cases 2 and 10; 30 mg. to the latter. Case 7 received 2 ampoules of 'lethidrone'. Case 9 received with his cocktail, presumably to prevent a hangover or in anticipation of one, a substance called 'valoid' (anti-emetic). Case 11 was classic. The patient received a potent conglomeration which induced respiratory and cardiac arrest. External cardiac massage was instituted and with this was combined a potent vasopressor. Many of the above patients with such sequences must have been on the verge of dissolution, and one of these certainly had the luckiest escape from death imaginable![8]

Polypharmacy in the Postoperative Phase

There is no necessity for the anaesthetist, apart from prescribing for the relief of pain, to indulge in polypharmacy. He is, of course, in this phase an important member of the team and must concern himself with others in the treatment of postoperative shock and other untoward complications arising from anaesthesia and surgery.

Shock

In connection with the treatment of shock, attention must be drawn to the danger of noradrenaline infusion — especially its prolonged use. This much vaunted treatment has resulted from time to time in extensive, severe gangrenous ulceration. There should be little use, during anaesthesia or in the postoperative phase, of vasopressors of any kind, especially where rational anaesthetic techniques are employed and where combinations of drugs whose actions are unpredictable are avoided.

Vomiting

The incidence of vomiting in the postoperative phase has diminished greatly since anaesthetic techniques have improved and since the volatile anaesthetic agents like ether, chloroform, and trichlorethylene are not in such common use. Nevertheless, vomiting can be a most unpleasant sequel. The aetiology of vomiting is extremely complex and there may be a multiplicity of causes. It may arise from, but only very infrequently, a psychic factor, but it is quite unwarranted to prescribe as a prophylactic or therapeutic measure some form of tranquillizer in every case. This again is irrational because in the vast majority of cases vomiting results from manipulation or cutting of abdominal viscera or from gastric irritation of drugs. As nature's way of excretion of toxins, it may thus be beneficial. If vomiting becomes severe and results in dehydration and electrolyte disturbance, treatment should be carried out by parental administration of appropriate solutions to restore electrolyte balance to normal. This is a much more physiological approach and certainly less harmful than to resort to tranquillizers with anti-emetic action, but with potential dangers of causing profound hypotension.

SUMMARY

1. Attention is drawn to the widespread use of drugs and drug combinations (polypharmacy) which induce iatrogenic disease. The anaesthetist must be cognizant of the manifestations of these conditions.

2. Dangers to anaesthetized patients suffering from diseases of medical progress are stressed because of completely altered physiological and pharmacological reactions in these patients to anaesthetic drugs.

3. Attention is drawn to the fact that patients are exposed to danger not only from irrational polypharmacy practised by physicians generally, but also by anaesthetists in the pre-operative, operative, and postoperative phases.

In conclusion I should like to plead for a 'puristic' outlook in anaesthetic practice, i.e. one opposed to the employment of multiple drugs by the anaesthetist. This is especially the case when patients, even before the administration of an anaesthetic, are disrupted psychologically and physiologically, not only by the stresses and strains of modern life, but also by iatrogenic disease.

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