ADVANCES IN FLUORINE CHEMISTRY

VOLUME 2

EDITORS

M. STACEY, F.R.S.
Mason Professor and Head of Department of Chemistry, University of Birmingham

J. C. TATLOW, Ph.D., D.Sc.
Professor of Organic Chemistry, University of Birmingham

A. G. SHARPE, M.A., Ph.D.
University Lecturer in Chemistry, Cambridge

WASHINGTON
BUTTERWORTHS
1961

[220] Templeton, D. H. and Dauben, C. H. *J. Amer. Chem. Soc.* 1953, **75**, 4560
[221] Carniglia, S. C. and Cunningham, B. B. *J. Amer. Chem. Soc.* 1955, **77**, 1451
[222] Westrum, E. F. and Eyring, L. *J. Amer. Chem. Soc.* 1951, **73**, 3396
[223] Feay, D. C. *Some Chemical Properties of Curium*, Thesis, University of California. See also *U.S.A.E.C. Report*, UCRL–2547, 1954
[224] Eyring, L., Cunningham, B. B. and Lohr, H. R. *J. Amer. Chem. Soc.* 1952, **74**, 1186
[225] Yakovlev, G. N. and Kosyakov, V. N. *Proc. 2nd U.N. Conf. Peaceful Uses Atomic Energy, Geneva*, 1958, paper 2127, 28, 373, 1958
[226] Asprey, L. B. and Keenan, T. K. *J. Inorg. Nuclear Chem.* 1958, **7**, 27
[227] Asprey, L. B., Ellinger, F. H. and Zachariasen, W. H. *J. Amer. Chem. Soc.* 1954, **76**, 5235
[228] Wallmann, J. C., Crane, W. W. T. and Cunningham, B. B. *J. Amer. Chem. Soc.* 1951, **73**, 493
[229] Asprey, L. B., Ellinger, F. H., Fried, S. and Zachariasen, W. H. *J. Amer. Chem. Soc.* 1957, **79**, 5825
[230] Asprey, L. B. and Ellinger, F. H. *U.S.A.E.C. Report*, AECD–3627, declassified 1954
[231] Crane, W. W. T. *U.S.A.E.C. Report*, UCRL–1220, 1951

THE PHYSIOLOGICAL ACTION OF ORGANIC COMPOUNDS CONTAINING FLUORINE

B. C. SAUNDERS

University Chemical Laboratory, Cambridge, England

INTRODUCTION

This chapter is concerned mainly with a description of the toxic action of certain classes of organic compounds containing fluorine. It is, however, obvious that in much of the literature the term 'fluorine poisoning' is used in a vague way to cover a variety of conditions that are totally unrelated pharmacologically. For this reason, and in order to gain an overall picture of the pharmacological principles involved, we start with a brief reference to poisoning by elementary fluorine and by hydrogen fluoride. A description is then given of the effect of the fluoride ion (F^-). Large doses of fluoride ion are the cause of true *fluoride poisoning*, often known as *fluorosis* when the condition is chronic.

The study of the toxic action of inorganic fluorides is currently being pursued in connexion with the fluoridation of domestic water supplies in the

treatment of dental caries. Therefore a brief consideration of dental caries is apposite.

The examination of toxic organic compounds containing fluorine is of comparatively recent origin and stems from very extensive investigations in connexion with the production of potential chemical warfare agents during World War II. Two main types of organo-fluorine compound, having entirely different actions, have emerged: (i) those containing the P—F link as typified by the phosphorofluoridates, and (ii) those containing the C—F link as exemplified by the fluoroacetates. Most of the chapter is devoted to a detailed discussion of these two important classes. Although consideration of toxic phenomena is the primary purpose of the chapter, brief details are also given, where appropriate, of the chemistry of some of the more important organic compounds. Only in this way can a true understanding of the pharmacological action be established.

It should be made clear to the reader at the outset that, although organophosphorus compounds containing the P—F link (class i above) are toxic, there are nevertheless many organo-phosphorus compounds not containing fluorine that do indeed show similar toxic properties. The molecular structural requirements for toxicity among organo-phosphorus derivatives will therefore be discussed in detail and the important part played by the fluorine atom in the organo-phosphorus molecule will be made clear (see pages 195–196).

As a result of the detailed study of the mode of action of toxic fluorine compounds, important fundamental principles have emerged. As a consequence, peacetime applications have been developed and they are proving of great value to mankind. Thus the reader can be assured that the ultimate goal of these toxicity studies has proved to be not the taking, but the saving, of human life.

TOXIC PROPERTIES OF FLUORINE AND OF HYDROGEN FLUORIDE

These gases rank as corrosive poisons. They burn away the mucous membranes in the mouth, throat, bronchi, bronchioles, lungs and stomach, and cause vomiting and great pain. Water is lost from the blood which becomes concentrated. As a result there is a fall in blood pressure. Secretion of saliva and urine ceases and death may follow from failure of circulation.

Elementary fluorine, b.p. −187°C, is an extremely active substance. As it reacts with a large number of organic compounds, it is not surprising that even small traces will act on the eyes and on the mucous membranes generally. Contact with the skin causes severe burns and destroys tissues.

Fluorine attacks water liberating hydrogen fluoride which is itself toxic. Moreover contact with body fluids, which contain sodium chloride, will liberate chlorine. Chlorine itself is a lung irritant and when it reaches the bronchioles and alveoli causes pulmonary oedema. Thus, either by direct or indirect action, fluorine is a corrosive poison of the first magnitude, especially by inhalation.

Hydrogen fluoride (b.p. 19·5°C) is also very dangerous because of the corrosive nature of the vapour and liquid. A drop of the liquid in contact

with the skin causes painful ulcers. A very dilute solution of the acid, however, causes no ill effects by temporary contact with the skin. Undissociated hydrogen fluoride appears to be able to penetrate through intact epidermis. Local injection of a solution of calcium gluconate can often arrest the process[1]. Immediate washing with water and with dilute ammonia, however, should always be the initial emergency treatment.

METALLIC FLUORIDES

Fluorides are widely distributed in animal tissues, particularly in bones and teeth. Fresh bone contains 100–300 mg of fluorides per kilogram. The average diet of man supplies 0·2–0·3 mg per day, exclusive of drinking water[2] (see below). The upper safe limit of urinary excretion is estimated as 5 mg per day.

Fluorides are readily absorbed by the body, but are excreted slowly and are therefore prone to cause cumulative poisoning. Fluorides are powerful inhibitors of many enzymic reactions. For example, there is marked inhibitory action towards enzymes concerned with glycolysis. Lipase, various esterases, urease, bone phosphatase, succinic dehydrogenase and catalase are all inhibited. Fluoride greatly retards peroxidase action and as the thyroid gland is known to contain a peroxidase, it is to be expected that fluoride poisoning will therefore affect metabolism generally, including certain phosphorylation processes. The symptoms of acute poisoning noted below will therefore, in the main, result from these very widespread enzymic inhibitions. Salivary amylase, however, is not affected even by fairly high concentrations of fluoride.[3]

Sodium fluoride

Sodium fluoride is incorporated in many powders designed to kill cockroaches, mice and rats. At one time it was used as a food preservative, but it is much too dangerous for this purpose. Many cases of poisoning of human beings by sodium fluoride have been recorded. For the most part acute poisoning has been accidental. The mouse and rat poisons containing sodium fluoride have been accidentally used on a few occasions in cooking. A case is recorded of 47 out of 263 patients dying in a hospital after eating food in which sodium fluoride had been incorporated[4]. The symptoms were numbness of the mouth, nausea, vomiting, diarrhœa and abdominal cramps leading to collapse within 2 to 4 hours. The food contained from 3·2 to 13 per cent of sodium fluoride. This, of course, represents a massive dose compared with the lethal doses of phosphorofluoridates (pages 188–189) and of fluoroacetates (pages 196–198).

Other recorded fatal cases include the accidental ingestion of a teaspoonful of sodium fluoride in mistake for Epsom salts[5].

The lethal dose for adults is estimated at between 5 g and 10 g, and a dose of 17 g is calculated to kill within one hour[6]. Dangerous symptoms arise from a dose of 0·25 g. In general, the ingestion of the soluble fluoride ion causes severe acute gastroenteritis and vomiting referred to above. The vomitus is often bloody. Intense thirst, convulsions and spasms are very common symptoms.

The ingestion of sublethal doses often leads to nephritis and injury to the liver (jaundice).

Intravenous injection of an aqueous solution of fluoride causes thirst, abdominal pains and diuresis. Nitrogen excretion is raised and the total metabolism reduced with hypocalcaemia. Injury to the capillaries takes place, the permeability of which is increased even by small doses. Fluoride is secreted into the milk, enough in fact to kill nursling rats. It passes easily across the placenta into the foetus.

The above observations with regard to sodium fluoride apply in the main also to sodium fluorosilicate, Na_2SiF_6, which is used as a rat poison. It has produced fatalities in man. It is decomposed by water to sodium fluoride and silicon tetrafluoride, SiF_4. Gaseous silicon tetrafluoride is decomposed in moist air passages to hydrogen fluoride and H_2SiF_6. The latter then gives silica which is deposited in the air passages.

Treatment of acute fluoride poisoning

Gastric lavage must be administered without delay. Drinking of lime water or calcium chloride solution in order to precipitate the soluble fluoride as insoluble calcium fluoride is advised. The slow intravenous injection of a soluble calcium salt (e.g. calcium gluconate) is also recommended[7]. Morphine in 10 mg doses and the intravenous injection of 50 ml of 50 per cent glucose solution may become necessary[8]. Chemically, fluoride poisoning is detected by an excess of F^- in the vomit or in the urine.

Chronic poisoning by sodium fluoride (fluorosis)

The feeding of very small doses of the order of 15 to 150 mg per kilogram body weight per day to experimental animals produces symptoms of chronic poisoning[9]. Growth is retarded, the oestrous cycle and reproduction are inhibited, the pituitary and thyroid glands are affected and structural changes occur in the bones and teeth (see below). Chronic toxicity by inorganic fluoride is due mainly to interference with calcium and phosphorus metabolism and results in the depletion of calcium due to the formation of insoluble calcium fluoride and a deranged calcium-phosphorus balance. This often leads to osteroscleroses and ultimately to changes in bone marrow that result in anaemia and loss in weight. Furthermore, one essential stage in the clotting of blood is the interaction of thrombokinase and prothrombin to form thrombin. This conversion does not take place in the absence of calcium ions, therefore excessive amounts of fluoride in the blood stream will decrease blood-clotting power.

Another symptom of chronic fluorine poisoning is the mottling of the enamel of the teeth (*Figure 1*).

Fluorosis develops in workers exposed to the dust of cryolite, CaF_2, or phosphate rock if the daily intake exceeds about 20 mg of fluoride per day.

It is well established that when fluoride occurs in large amounts in soil or water a chronic endemic fluorosis is likely to occur particularly among cattle and sheep[10]. Contamination by dust is also likely to occur in the vicinity of certain industries such as cement works, potteries, etc. The chief symptom is lameness and secondarily affection of the teeth. The use of ground rock phosphate in mineral supplements in livestock feeding has

resulted in outbreaks of fluorosis from time to time, so that it is now the modern commercial practice to use 'defluorinated' phosphates containing 0·1–0·5 per cent of fluorine. Such products are innocuous.

Sodium fluoride has been used as an anthelmintic against round-worms in pigs, for which purpose it is usually mixed with dry food in a concentration not exceeding 1 per cent. A concentration of 5 per cent is extremely toxic and fatal to pigs.

The problem of dental caries

The relationship between the incidence of the mottling of the enamel of human teeth and the composition of drinking water was first definitely established in 1931[11] although many earlier observations have been recorded. It was shown that mottling was very common in areas where the drinking water contained 2·0 to 13·7 parts per million of sodium fluoride. On the other hand when the drinking water contains no fluoride whatsoever the incidence of dental caries is high. This led to extensive studies to determine whether a concentration of drinking water could be found which would result in a significant reduction in the incidence of dental caries and at the same time produce negligible mottling of the enamel of teeth. It has been suggested by some authorities that fluoridation of water up to a concentration of 1 part per million of sodium fluoride is a reasonably safe and effective measure[12], but see below.

It should be noted that dental caries is a common disease of civilized man who is living more and more on refined and processed foods, and it is evident that nutrition plays an important part in dental decay. It has been recorded that tooth decay can be produced in the white rat fed on a controlled artificial diet and that caries producible by such a diet is prevented when sodium fluoride is fed simultaneously in small quantities.

There is a very extensive literature on the effects of fluoride on teeth and on bone. As indicated above, the effects on teeth are both protective and harmful. The beneficial anticariogenic action of traces of fluoride appears to depend upon three distinct factors[13]: (i) the formation of fluoroapatite, $3Ca_3(PO_4)_2$, CaF_2, on the enamel of the tooth and that this compound is more resistant to acid erosion than the hydroxyapatite, $3Ca_3(PO_4)_2$, $Ca(OH)_2$, or carbonate apatite, $3Ca_3(PO_4)_2$, $CaCO_3$, that it replaces; (ii) antibacterial action; (iii) anti-enzymic action within the oral cavity. It is known, for example, that certain phosphatases are present in human saliva and these, according to some workers, are responsible for the decalcification of teeth.

The mechanism of the mottling of teeth is not well understood. It seems, however, that the brown stain of mottled enamel is caused by manganese[14] and that its incorporation in the apatite molecule is facilitated in some unknown way by excess of fluoride ion.

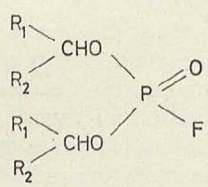
The artificial fluoridation of public water supplies as a means of combating tooth decay presents an extremely controversial problem. Sharp differences of opinion have been expressed by dental surgeons, health organizations, pharmacologists and biochemists. Steyn[15], who gives some 580 literature references, expresses the view that widespread artificial fluoridation should not be undertaken at present. Among reasons advanced by him are:

(1) divergent experimental findings; (2) the concentration of fluoride recommended as prophylaxis against dental caries is dangerously near the concentration that causes chronic fluorosis; (3) it is inadvisable to permit millions of people, irrespective of age, sex, susceptibility, disease, etc., to consume water containing the same concentration of fluoride; (4) topical application of metallic fluorides is safer and equally effective.

Whatever view one may take of these observations, it is clear that we ought to know a good deal more about the precise effect of the fluoride ion on as large a range of tissues as possible and over a period of many years before submitting whole communities to the treatment. That fluoride is an essential element for the mammalian body is obvious. The problem is one of control of supply. A recent report of the World Health Organization[16] is, however, reassuring and concludes that the controlled fluoridation of public water supplies involves no hazard.

PHOSPHOROFLUORIDATES

At the beginning of World War II a series of dialkyl phosphorofluoridates (I) was synthesized by Cambridge workers by methods indicated in outline later. These compounds are colourless, stable, almost odourless, non-corrosive liquids. With them tests were carried out according to established



(I)

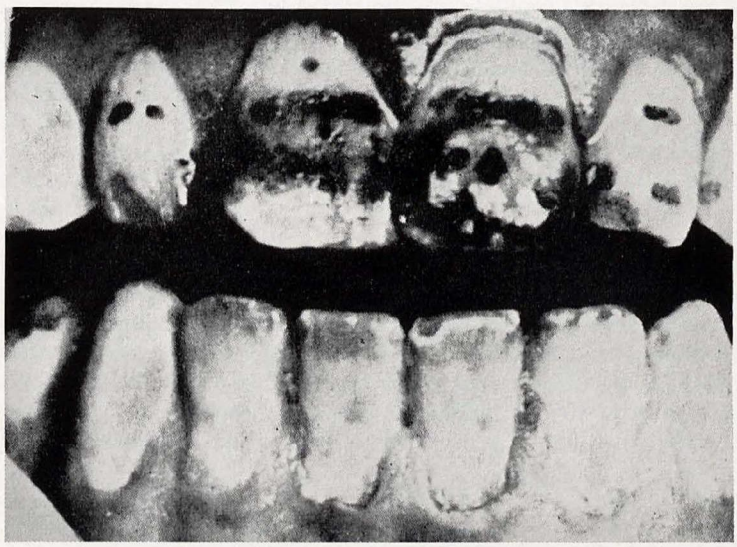
procedures on (*a*) small animals, (*b*) human beings, and (*c*) enzyme systems. An important compound of the series, synthesized[17] in 1941, which has attracted a great deal of attention is diisopropyl phosphorofluoridate (I, $R_1 = R_2 = Me$), often referred to as D.F.P. The compound, b.p. 183°, f.p. −82°, does not attack glass and is hydrolysed only very slowly by water. The original observers (Saunders and his colleagues[17]) entered a 10 m^3 glass testing-chamber in which D.F.P. was sprayed at a concentration of 1 in 1,000,000 (i.e. 0·0082 mg/l.), and remained inside for 5 minutes. Practically no effects were noted during exposure nor until some 5 minutes later. Intense myosis then set in and often persisted for 7 days, with little relaxation of symptoms under 72 hours. This myotic effect took the following course:

(1) Pupil constriction, often to pin-point size (*Figure 2*). The amount of light entering the eye was greatly reduced.

(2) Powers of accommodation were affected.

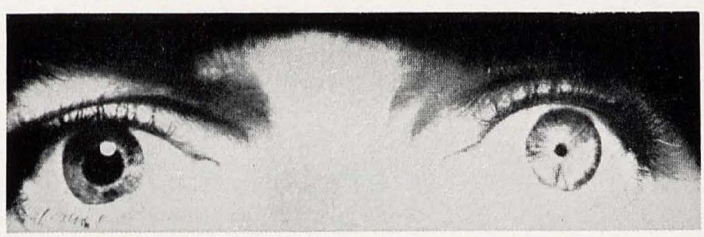
(3) Photophobia and headaches, and pain experienced when changing to light of different intensity.

At higher concentrations a quick 'knock-out' action resulted. The L.C. 50

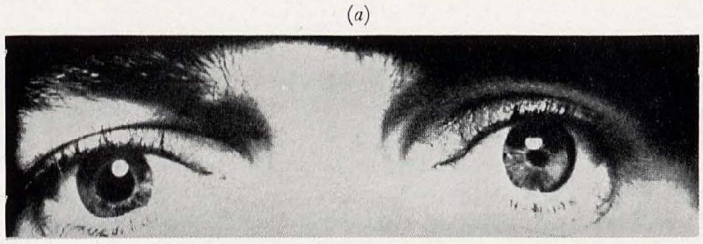


(By courtesy of Dr. T. Ockerse)

Figure 1. Teeth showing a severe degree of mottling as a result of damage by fluorine in drinking water



(*a*)



(*b*)

(By courtesy of Cambridge University Press, from *Phosphorus and Fluorine* by Dr. B. C. Saunders, 1957)

Figure 2. Pupil sizes. Left eye exposed to di-isopropyl phosphorofluoridate (0·008 mg/l.; 2 min *exposure*) *:* (a) 3 h *after exposure;* (b) 24 h *after exposure*

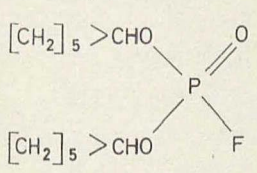
To face p. 183

for 10 minute exposures* was 0·36 mg/l. for rats and 0·44 mg/l. for mice. This means that D.F.P. is more toxic than chloropicrin and comparable with hydrogen cyanide. The symptoms were muscular cramps, gasping and finally cessation of respiration.

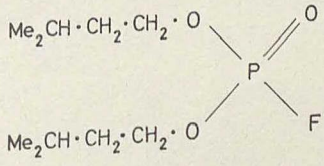
The compound is also toxic by injection†, thus for intravenous injection into rabbits the L.D. 50 was about 0·5 mg/kg. Pupil constriction began two minutes after injection, followed by loss of muscular co-ordination and then by respiratory collapse.

Relationship between physiological action and chemical constitution

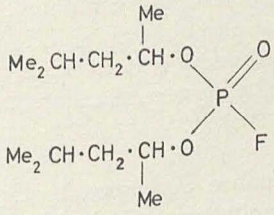
The relationship between physiological effects and chemical constitution was studied in detail[18] and it was shown that the more potent compounds are derived from secondary alcohols. Thus diisopropyl phosphorofluoridate is more potent than either diethyl or di-*n*-propyl phosphorofluoridate, and the toxicity of dicyclohexyl phosphorofluoridate (II) is of a high order (L.C. 50 for mice, rats and rabbits was 0·11 mg/l.). Di-*n*-butyl phosphoro-



(II)



(III)



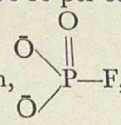
(IV)

fluoridate was weakly toxic and produced only feeble myosis, whereas di-*sec*-butyl phosphorofluoridate (1, $R_1 = Me$, $R_2 = Et$) was comparable with D.F.P. Investigations were made to determine whether branching of the chain adjacent to the oxygen atom was necessary for high toxicity or whether branching at the end of the chain would do equally well. Accordingly diisoamyl phosphorofluoridate (III) was synthesized and found to be only slightly toxic, and almost devoid of myotic properties. A striking result was obtained with the compound derived by branching the chain in (III) by a methyl group on carbon atom 1. This new compound (IV) was very toxic and with strong myotic action. Thus a secondary grouping seems to be essential for high toxicity.

* Toxicity by inhalation (L.C. 50) is expressed as the concentration in mg per litre required to kill 50 per cent of the animals exposed.

† Toxicity by injection (L.D. 50) is expressed as the dose in mg per kg body weight required to kill 50 per cent of the animals.

In the type of molecule under discussion, $(RO)_2POX$, it was clearly shown[18] that whereas toxicity is high if X = F, myotic effect is absent and toxicity low if X = H, Me, Et, OH, OEt, OCH_2CH_2Cl, Cl, NH_2, NHMe, NHPh, CH_2F, CH_2CH_2F, CN, SCN, etc. Thus in this series the single fluorine attached directly to phosphorus is playing some very significant part. This point is enlarged upon later. Toxicity is also low in the aromatic series (for example, diphenyl phosphorofluoridate). Furthermore, the difluoro-compound, $(EtO)POF_2$, had neither myotic nor toxic action[19].

The first investigation on the action of phosphorofluoridates on enzymes were carried out in Cambridge in 1941. It was shown that these esters inhibit the action of cholinesterase, which hydrolyses acetylcholine. Diisopropyl phosphorofluoridate is active against the enzyme in extremely low concentrations (of the order of 10^{-9} M against 'pseudo' cholinesterase and *ca.* 10^{-7} M against 'true' cholinesterase*). This inhibition was not due to fluoride ion (produced by hydrolysis) as sodium fluoride required a high concentration, namely 10^{-2} M, to give 50 per cent inhibition of cholinesterase activity. Similarly a 10^{-2} M solution of ammonium phosphorofluoridate was also necessary to give 50 per cent inhibition: that is to say that the free phosphorofluoridate ion,  , is ineffective. The naturally occurring alkaloid eserine, which contains neither fluorine nor phosphorus, has been known for a long time as a strong inhibitor of cholinesterase, but even here a concentration of 10^{-8} M is required; moreover its action is reversible, whereas that of D.F.P. is irreversible. Saunders and Worthy[22] prepared D.F.P. containing radioactive phosphorus, ^{32}P. This enabled Boursnell and Webb[23] to show that approximately one molecule of D.F.P. combines with one molecule of enzyme producing complete inactivation.

Synthetic methods

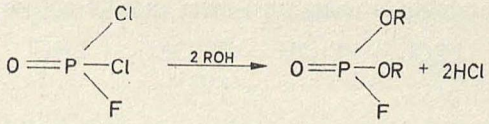
One very successful procedure developed by British workers (Saunders and Stacey[24]) consisted in treating an alcohol with phosphorus trichloride and then with chlorine giving the dialkyl phosphorochloridate in high yield; the latter on being heated with sodium fluoride readily gave the dialkyl phosphorofluoridate. It thus became possible to prepare phosphorofluoridates in excellent yield from cheap and readily accessible materials:

	Yield
$PCl_3 + 3ROH = (RO)_2POH + RCl + 2HCl$	89 per cent
$(RO)_2POH + Cl_2 = (RO)_2POCl + HCl$	80 per cent
$(RO)_2POCl + NaF = (RO)_2POF + NaCl$	84 per cent

Modifications were made in this 'hydrogen phosphite' method in order to put it on a technical scale and it was shown that it could be run virtually as a *one-stage* process. The process was patented and was employed in Great Britain and later in America for the production of D.F.P. and similar compounds.

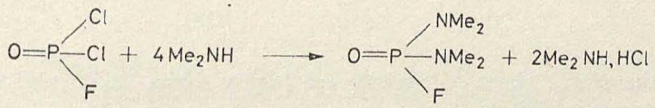
* Broadly speaking, 'true' cholinesterase occurs in erythrocytes and brain, and 'pseudo' cholinesterase in serum[21].

An alternative method consisted in the partial fluorination of phosphorus oxychloride to give phosphorus oxydichlorofluoride, $POCl_2F$. In the latter, the chlorine atoms are much more reactive than the fluorine atom, and with an alcohol the dialkyl phosphorofluoridate is readily obtained in high yield[26].



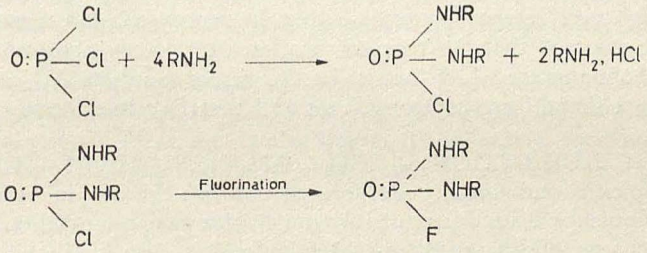
This reaction cannot compete with the 'hydrogen phosphite' method for large-scale work, nevertheless it is valuable for exploratory purposes. In particular, it is possible to prepare diaryl phosphorofluoridates and dialkyl phosphorofluoridodithiolates $[(RS)_2POF]$ by the action of $POCl_2F$ on the appropriate phenol or mercaptan.

In 1942 a new type of phosphorus-fluorine compound was obtained from $POCl_2F$ and an amine[27]. In the condensation only the chlorine atoms were replaced:

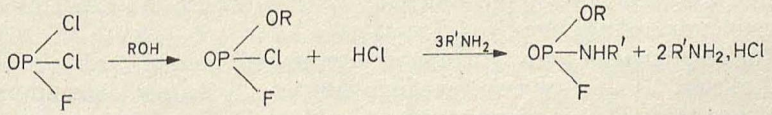


(V)

The reaction was extended to the preparation of a large range of phosphorodiamidic fluorides, many of which were toxic, thus tetramethyl phosphorodiamidic fluoride (V) had an L.C. 50 of 0·2 mg/l. They were, however, unlike the phosphorofluoridic esters, devoid of myotic action. About this time an alternative preparation was developed as follows[28]:



The toxicities of a phosphorofluoridic ester were 'combined' with that of a phosphorodiamidic fluoride in a 'hybrid' molecule, and the following synthesis effected in 1943[28]:



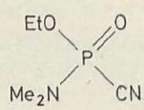
(VI)

This type of compound (an ethyl N-substituted phosphoroamidofluoridate, VI) was highly toxic.

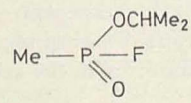
For purposes of comparison, a compound (VII) of a lower state of oxidation was obtained by the action of phosphorus dichlorofluoride on ethyl alcohol. The new compound, a phosphorofluoridite, unlike the phosphorofluoridate, was unstable to water, non-toxic and did not produce myosis.

$$FPCl_2 + 2EtOH = FP(OEt)_2 + 2HCl$$
(VII)

During World War II German workers, particularly Schrader[29], investigated organo-phosphorus compounds. It need hardly be said that this work was quite independent of British activities. Factories for the production of the potential war gases tabun (VIII) and sarin (IX) were in operation at the



(VIII)



(IX)

end of the war. These 'G' agents are highly toxic, being very powerful cholinesterase inhibitors.

Cause of toxic action of P—F compounds

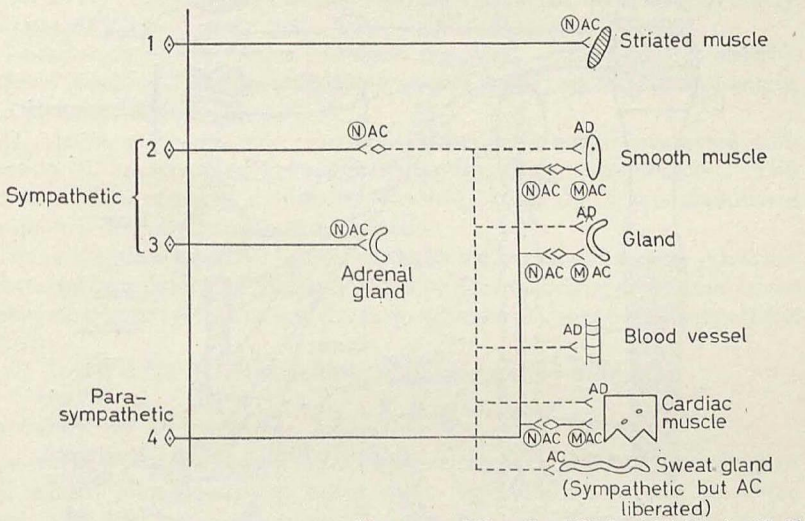
It was stated above that certain organophosphorus compounds (often called nerve gases) show anticholinesterase activity. We will now consider what this means, and describe in general terms what happens at the junction of the nerve ending of a mammalian motor fibre and striated (voluntary) muscle. On stimulating the nerve, acetylcholine, $Me_3N^+CH_2CH_2OCOCH_3$, (AC), is liberated as represented diagrammatically in *Figure 3*. The AC then alights on 'receptor' patches within the muscle causing contraction. It may be assumed that the receptor patches can exactly accommodate AC. Now cholinesterase which occurs in the tissues converts AC into choline (incorrect shape for receptor patches and therefore ineffective) and acetic acid:

$$Me_3N^+CH_2CH_2OCOCH_3 + H_2O = Me_3N^+CH_2CH_2OH + CH_3COOH$$

A complex is undoubtedly first formed between the enzyme and AC, and this complex will itself presumably not fit the receptor patches. (Incidentally, curare, which paralyses motor end-plates, also fits into the receptor patches and thereby excludes the entry of acetylcholine. Curare itself, however, has no direct action on muscle.) Thus a nerve gas causes acetylcholine to accumulate, and therefore, among other actions, will cause intense contraction of striated muscle. In this respect the effect of AC resembles that of nicotine (N) (*Figure 3*).

The autonomic nervous system innervates smooth muscle, cardiac muscle and glands. It thus governs functions that usually do not obtrude upon consciousness. The autonomic system has two divisions, (*a*) sympathetic and (*b*) parasympathetic, with complementary or antagonistic actions. Thus

stimulation of the parasympathetic system causes the pupils to contract, the heart to beat more slowly, etc. The sympathetic system causes opposite effects. AC is liberated at the ends of parasympathetic nerve fibres whereas adrenalin or noradrenalin is liberated at the ends of sympathetic fibres[30] (*Figure 3*). Thus, since a nerve gas has anticholinesterase activity it potentiates parasympathetic activity and so is known as a parasympathomimetic



(By courtesy of Chem. Soc. 1957, Special Publication No. 8)

Figure 3. Diagram of the human nervous system: 1, *voluntary system;* 2, 3, 4, *autonomic (involuntary) nervous system;* AC, *liberation of acetylcholine;* AD, *liberation of adrenalin or noradrenalin*

agent. When the reinforcement of parasympathetic activity is sufficiently great, the animal dies. The action of muscarine resembles that of acetylcholine at the termination of a post-ganglionic parasympathetic fibre (M, *Figure 3*).

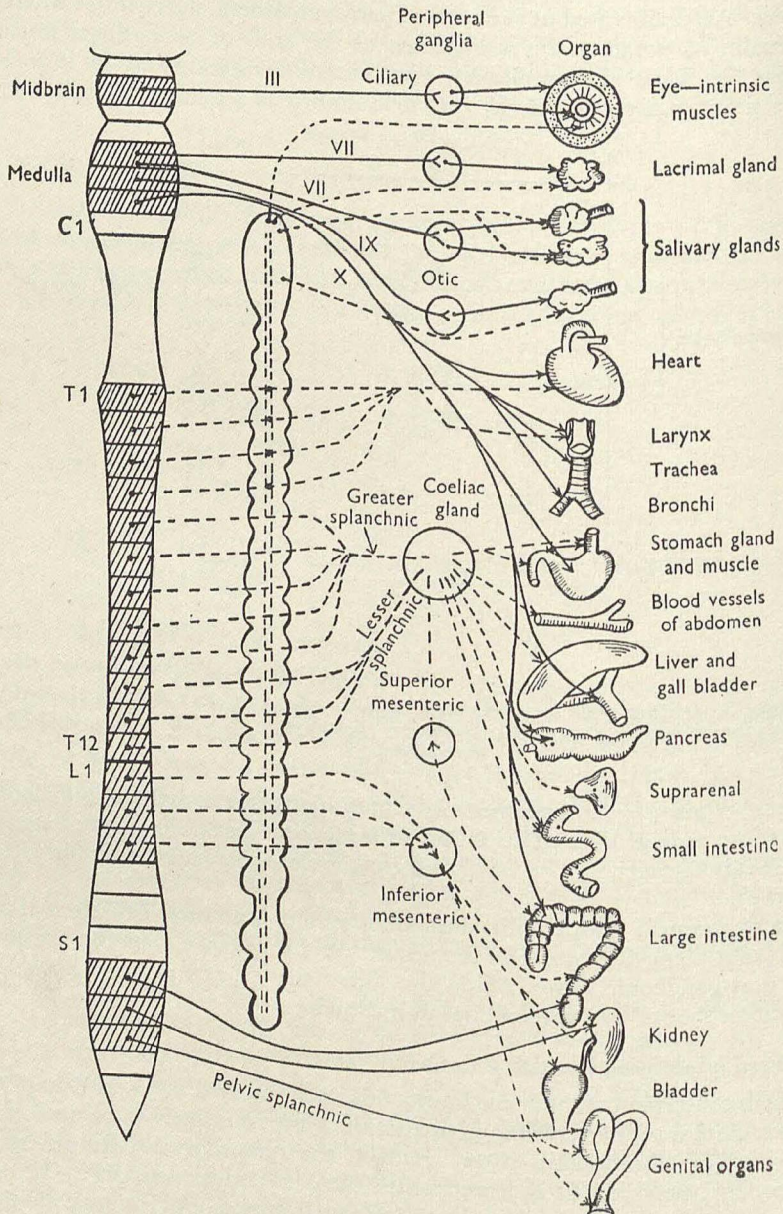
An anatomical feature of the autonomic system is an intermediate synapse at a point along the course of the nerve. At this synapse, between the pre- and post-ganglionic fibres, AC is also liberated; its action here, however, resembles that of nicotine and not of muscarine.

Symptoms of phosphorofluoridate poisoning

If a detailed plan of the human autonomic nervous system[31] were examined (*Figure 4*), it would be possible to predict the symptoms likely to be produced by parasympathomimetic drugs. In fact, the symptoms usually observed (recorded below) do fit in exactly with the anatomical analysis[32]. In addition, it is convenient to describe the effects in terms of (1) muscarine-like action (M in *Figure 3*), (3) nicotine-like action (N), and (2) central action.

(1) *Eye*[33]—Myosis, very sensitive reaction by direct action, inhalation, and injection. Loss of powers of accommodation.

Lacrimal and salivary glands—Increased secretion, not noticeable with low concentrations.



(By courtesy of Cambridge University Press, from *Phosphorus and Fluorine* by B. C. Saunders, 1957)

Figure 4. Plan of the autonomic nervous system (after Gray)

Heart—Bradycardia.

Bronchioles—Constriction, difficulty in breathing even with low doses, gasping and finally cessation of respiration (usually the immediate cause of death).

Alimentary canal—Initial glandular secretion, vomiting and diarrhoea follow. The lumen of the gut is constricted, especially rectum (hence the use of D.F.P. for treatment of post-operative paralytic ileus, see page 204).

Urinary bladder—Constriction, hence urinary frequency.

Genital organs—Stimulation via 'nervi erigentes'.

Sweat glands—Although sympathetic anatomically, are in fact cholinergic, and therefore stimulated.

(2) *Action at neuromuscular junctions*—Muscular cramps: sustained contraction of intercostal muscles, rendering breathing more difficult. This nicotine effect requires a higher concentration of the organophosphorus compound than does the muscarine action.

Demyelination of nerve fibres can also take place and this adversely affects the functioning of any part of the peripheral voluntary system, of the parasympathetic system, and of the preganglionic portions of the sympathetic system.

(3) *Central effects*—Hallucinations, nightmares and headaches.

Treatment

Muscarine-like effects are relieved to some extent by atropine, homatropine and related parasympathetic antagonists: injection is necessary in severe cases, and instillation of ointments for mild cases of myosis. Ephedrine relieves bronchospasm. Artificial respiration is necessary with severe poisoning. Central effects are antagonized to some extent by atropine, analgesics, and certain depressants of the central nervous system.

The work of Wilson[34], Berry, Davies and Green[35] and Hobbiger[36] on the detoxicating effect of hydroxylamine, oximes and related compounds on anticholinesterases will undoubtedly play an important part in therapy as more becomes known of their precise mode of action and toxic side-reactions.

Preganglionic fibres of the sympathetic system and also the synapses at the adrenal gland are cholinergic (see *Figure 3*). This must mean that, in severe poisoning, the sympathetic system is also rendered extremely active, thus the entire nervous system is thrown into chaos. This aspect of organophosphorus poisoning has received little attention.

Besides compounds of the type $(RO)_2POX$ in which X = F, toxicity and anticholinesterase activity are observed when X represents an anhydride structure of a certain type, e.g. tetralkyl pyrophosphates,

(T.E.P.P.) $(EtO)_2P(=O)—O—P(=O)(OEt)_2$

p-nitrophenyl esters, etc.

Nevertheless the fluorine atom in $(RO)_2POF$ cannot be replaced by other halogens without loss of toxicity. Hence the fluorine atom must have some essential property that enables it to 'complex' readily with cholinesterase. Such a property might be the formation of a hydrogen bond between the

fluorine atom and a hydrogen atom of the enzyme. The 'positive' phosphorus atom then attacks the enzyme with elimination of HF. Such hydrogen bond

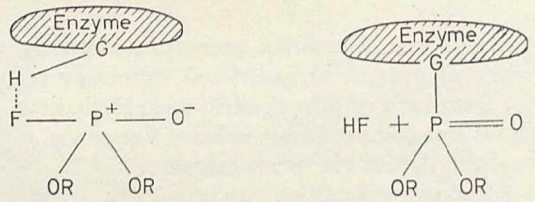


Figure 5

formation is not likely with the phosphorochloridate which has been shown to be non-toxic, but certain other phosphate esters containing oxygen, nitrogen or sulphur could readily participate in hydrogen bond formation.

It is not surprising then that pyrophosphates, *p*-nitrophenyl phosphate esters and compounds such as

$$(EtO)_2P(=O)—SCH_2CH_2NEt_2$$

are powerful cholinesterase inhibitors. In the writer's view, the anhydride structure is in itself probably not essential, but what may be important is the ability to form hydrogen bonds as outlined above. This is a property possessed by fluorine to an excellent degree. Many cholinesterase inhibitors show an early and reversible stage of poisoning, followed by a permanent and irreversible effect[37]. It is very inviting to suggest that hydrogen bonding is concerned with this essential but transitory first stage, and that true phosphorylation is a consequential process.

FLUOROACETATES

The term 'fluoroacetates' is often applied loosely to compounds containing the $—CH_2F$ group and related chemically to fluoroacetic acid.

Apart from early work by Swarts[38] and certain Polish workers, these compounds attracted little serious attention before the war. Methyl fluoroacetate (M.F.A.) was the first compound to be investigated in detail[39]. When methyl chloroacetate and potassium fluoride were heated together in an inclined rotating autoclave at 220°, a high yield of M.F.A. was obtained. Methods not involving an autoclave have been suggested, but usually yields of pure material are lower.

M.F.A., a stable mobile liquid, b.p. 104°, has an extremely faint odour. Animals did not usually exhibit any symptoms during exposure to lethal concentrations of the vapour, and no obvious effects were noted for 30–60 minutes (depending upon the concentration) after exposure. Convulsions then took place and death usually followed within a few hours. For rabbits and guinea-pigs, the L.C. 50 for a 10-minute exposure was about 0·1 mg/l. Mice were rather more resistant. Intravenous injection† produced symptoms

† See footnote on page 189.

similar to those displayed after exposure to the vapour. Even with large doses a delayed action was observed. The L.D. 50 for rabbits (intravenously) was about 0·25 mg/kg.

Relationship between physiological action and chemical constitution

It should be noted that, in the phosphorofluoridate series, the intensity of toxic action varies with the nature of the alcohol grouping whereas the toxicities of fluoroacetic acid, ethyl, *n*-propyl and iso-propyl fluoroacetates are similar to that of methyl fluoroacetate. On the other hand, methyl α-fluoropropionate, $CH_3 \cdot CHF \cdot COOCH_3$, and methyl α-fluoroisobutyrate, $(CH_3)_2CF \cdot COOCH_3$, showed negligible toxicity. It is significant that these compounds do not contain the FCH_2CO- group. The acids $F_2CH \cdot COOH$ and $F_3C \cdot COOH$ and their esters are non-toxic.

Sodium fluoroacetate was prepared as a stable water-soluble compound containing the FCH_2CO- group, suitable for animal-feeding experiments[39]. This salt is now finding application to some extent as a rodenticide (called 1088), but if used in this way very great care must be taken to keep it away from human beings and domestic animals.

The following acyl halides were examined:

ACYL HALIDES

Fluoroacetyl chloride	FCH_2COCl	Toxicity similar to that of M.F.A.
Chloroacetyl fluoride	$ClCH_2COF$	Non-toxic
Fluoroacetyl fluoride	FCH_2COF	Toxicity similar to that of M.F.A.

These results were in accordance with expectation, and it thus became clear that the toxicity was connected with the FCH_2CO— group whereas the

O
‖
—C—F group was ineffective. Additional confirmation was provided by the observation that ethyl fluoroformate, $FCOOC_2H_5$ (also containing the

O
‖
—C—F group), was non-toxic.

Fluoroacetamide, FCH_2CONH_2, and the following substituted amides were all very similar convulsant poisons with delayed action: $FCH_2CONHCH_3$, $FCH_2CON(NO)CH_3$, $FCH_2CONHCH_2CH_2OH$, $FCH_2CONHCH_2CH_2Cl$, $FCH_2CON(CH_2CH_2Cl)_2$. The magnitude of their toxicities suggested they were hydrolysed in the body to fluoroacetic acid[40]. In short, the effective part of the molecule was again FCH_2CO—.

Swarts[38] was unable to obtain fluoroethanol by any simple method. It was shown later by other workers[41] that, using the rotating autoclave, ethylene chlorohydrin could easily be fluorinated by potassium fluoride at 130°–135°. It should be noted that with sodium fluoride (in place of potassium fluoride) the yields were small. Fluoroethanol is a stable, mobile, colourless liquid of b.p. 101°. It is miscible with water and is practically odourless and tasteless. The compound is a convulsant poison and its toxicity is of the same order

as that of methyl fluoroacetate. With fluoroethanol and fluoroacetic acid as readily accessible starting materials a tremendous range of compounds, exhibiting varying degrees of toxic action, has been prepared.

Since fluoroethanol produced a toxic effect comparable with that of fluoroacetic acid, it seemed worth while synthesizing 2-fluoroethyl fluoroacetate, in which the 'active' parts of the two molecules were combined[39]. The compound possessed enhanced toxic properties: for a 10-minute exposure the L.C. 50 for rabbits by inhalation was 0·05 mg/l. Thus it was about twice as toxic as M.F.A. (weight for weight). This may indicate that the 2-fluoroethyl fluoroacetate molecule can perhaps exert some toxic action *per se*, independently of subsequent hydrolysis. The reason for this is not clear. In general, however, it seems that only those compounds are toxic that can give fluoroacetic acid either by oxidation and/or by hydrolysis[42].

Symptoms of fluoroacetate poisoning

Although the general feature of delayed action has been briefly referred to above, it should be emphasized that different species react differently[43]. Fluoroacetates are highly toxic to all mammals and should be looked upon as extremely dangerous chemicals. The L.D. 50 ranges from 0·1 mg per kg for dogs to 14 mg per kg for spider monkeys[44]. Rabbits, goats, horses and spider monkeys show only cardiac effects, myocardial depression, arrhythmias and ventricular fibrillation. Dogs and guinea-pigs show only central nervous effects giving rise to convulsions. Man, rhesus monkeys, cats and pigs show both reactions.

The immediate cause of death is cardiac failure, exhaustion from convulsions and toxic depression of the respiratory and vasomotor centres[45].

Cold blooded vertebrates are usually rather insensitive to fluoroacetate. On the other hand most insects are very sensitive, and as plants are not affected (page 199), fluoroacetates and related compounds have been suggested as insecticides (but see page 205). Seeds, however, especially of the tomato plant, appear to be affected[46].

Fluoroacetate is quite readily absorbed from the mammalian digestive tract and is then distributed fairly widely throughout the tissues. The part that does not undergo metabolism (page 202) is rapidly excreted through the urine and the gastrointestinal canal. A case is known of a sublethal dose of sodium fluoroacetate being taken orally by a human being and the urine subsequently being injected into a rat. The latter died from typical fluoroacetate poisoning.

The lethal dose of sodium fluoroacetate for man has been estimated at 5 mg per kg[47]. Such a dose has been administered to two horses, one orally and the other intravenously. The first horse died after 10 hours and the second after 5 hours. Apart from a thickening of the blood, it is claimed that there were no visible lesions after death. Dogs were then allowed to feed on the carcases. A dog that ate some of the heart died in 18 hours, whereas two that ate skeletal muscle and liver appeared to suffer no ill-effects.

A single intravenous dose of 0·4 mg of sodium fluoroacetate per kg given to sheep proved fatal within 4 to 6 hours. A sublethal dose of 0·2 mg/kg had little direct effect, but increased the susceptibility of the animals to further doses of fluoroacetate[48]. Thus two sheep that had received 0·2 mg/kg

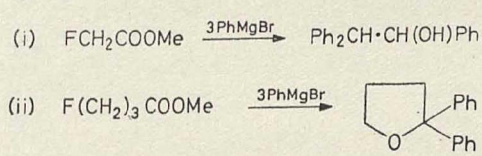
intravenously were given further doses of 0·2 mg/kg after 2 and 11 day intervals respectively. Both sheep died. This behaviour is opposite to that of the rat in which a sublethal dose produces some protection against further doses for some 36 hours.

Chemical stability of the C—F bond

The halogen atoms in chloroacetic, bromoacetic and iodoacetic acids are very reactive chemically and are readily removed by dilute alkali. Ethyl iodoacetate is a powerful lacrimator and is one of the typical tear gases still used for that purpose. Iodoacetates as a class inhibit metabolism and many of their pharmacological properties are attributable to the ready reaction between the reactive iodine atom and thiol groups. Monobromoacetic acid and monochloroacetic acid act similarly, but less effectively.

By comparison with the halogen atoms in the above monohalogenoacetic acids, the fluorine atom in monofluoroacetic acid is relatively firmly bound. For example, boiling 10 per cent aqueous sodium hydroxide produces no fluoride ion. This stability renders decontamination of 'fluoroacetates' difficult. For the same reason it is not easy to detect their presence by chemical means, and lack of odour enhances their insidious nature. It has recently been shown[49], however, that all 'fluoroacetates' are decomposed by boiling 30 per cent sodium hydroxide solution with the liberation of F^- ion. It is interesting to note that, under these conditions, the non-toxic trifluoroacetic acid gave no fluoride at all[49]. On the other hand when fluoroethanol was allowed to stand with cold 10 per cent aqueous sodium hydroxide overnight, fluorine was eliminated[50].

It has been demonstrated that Grignard reagents will liberate the F^- ion from 'fluoroacetates', e.g.



The fluorine atoms in trifluoroacetic acid are unaffected by Grignard reagents.

Naturally occurring fluoroacetate

The South African plant *dichapetalum cymosum* (gifblaar) contains potassium fluoroacetate[51] and hence is extremely poisonous to cattle who may eat the plant. Steyn[52] described gifblaar (*Figure 6*) as 'a heart poison, ranking amongst the most poisonous plants in the world. One seldom sees animals showing symptoms of gifblaar poisoning, as most of them die fairly soon after having ingested the plant, especially if they drink water. The disease is, as a rule, attended by muscular twitching, laboured breathing and weakness of the heart.' Steyn continues by saying that there are no specific post-mortem lesions. It is stated that less than an ounce of fresh leaves is enough to kill a sheep.

A letter from Mr. Snelling, Pretoria, has passed via Sir John le Rougetel, High Commissioner, Pretoria, to the author[53]. It contained the following information.

> *D. cymosum* grows in the Transvaal. In the spring, because of the depth of its roots and its access to deep water supplies, it is practically the first thing to turn green in the parched veldt. It grows in sandy country with boulders; its roots entwine round these boulders and it cannot be removed except by using dynamite. . . . Pole Evans once tried to get one out. He dug a quarry 100 ft. deep and even then couldn't get the thing disentangled. He advised farmers that the only thing to do was to fence in the areas where it grows. What interested him particularly was Saunders' statement that the toxic principle is a fluorine compound. For he says that it grows best precisely where the water has an abnormally high fluorine content, and especially around Warmbaths where there is so much fluorine in the water that it rots the teeth of the inhabitants and the whole town chews on its gums or dentures.

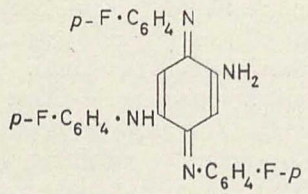
The chemical synthesis of fluoroacetic acid entails a high temperature reaction (page 196). It is not known how the plant builds up fluoroacetic acid, but it is fairly certain that it involves inorganic fluoride. (The observation of Dr. Pole Evans that the natural waters in the neighbourhood of the growing *cymosum* contain a high concentration of fluoride would support this idea.) The enzymes involved in this synthesis of fluoroacetic acid are not known, nor indeed the enzymes concerned with the reverse process, i.e. breaking of the C—F link. Presumably when the plant dies the fluoroacetate does not accumulate in the soil, but reverts to the fluoride ion. Although the C—F in fluoroacetates has not been broken by enzymes *in vitro*, it has been found possible to rupture the stable C—F link in the aromatic series by enzymic means (see below).

Dichapetalum toxicarium ('ratsbane' or 'broke back') is a shrub occurring in Sierra Leone[54]. The fruit is very poisonous and has been used for killing rats—hence the name 'ratsbane'. As it produces paralysis of the lower extremities it is also known as 'broke back'. One toxic principle of this plant[55] is most probably ω-fluoro-octadecenoic acid,

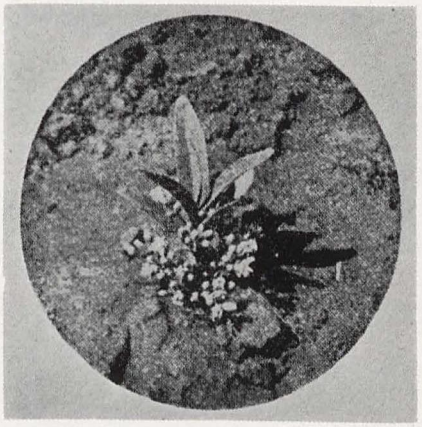
$$FCH_2(CH_2)_{7-n}CH = CH(CH_2)_{7+n}COOH$$

Enzymic cleavage of a C—F bond

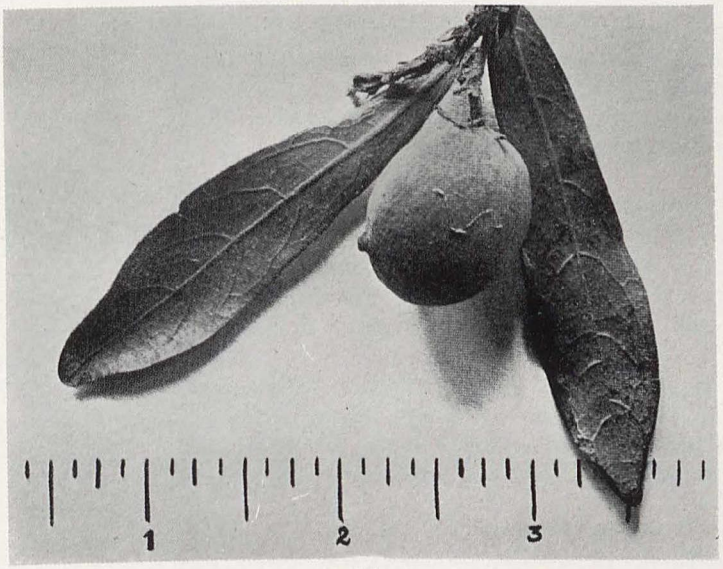
In the course of detailed investigations on peroxidase-catalysed oxidations[56], a facile enzymic cleavage of the C—F bond in *p*-fluoroaniline has been discovered[57]. In acetate buffer (pH 4·5) and at room temperature the amine was oxidized by hydrogen peroxide and the enzyme peroxidase to the red crystalline 2-amino-5-*p*-fluoroanilinobenzoquinone di-*p*-fluoroanil (X).



(X)



(*a*)



(*b*)

(By courtesy of *Fmg in S. Afr.* 1939, **14**, 285)

Figure 6. Dichapetalum cymosum (gifblaar): (a) *whole plant;* (b) *fruit and leaves. Leaves are alternate and finely veined*

To face p. 200

The formation of (X) requires the elimination of one fluorine atom per four molecules of amine. The fluorine was expelled as F^-. This oxidation of *p*-fluoroaniline is the first recorded case of an enzymic cleavage of a C—F bond by a single enzyme.

Alternating toxicities

A most striking alternation in the toxic properties of ω-fluorocarboxylic esters has been demonstrated as follows (Saunders[58]):

FCH_2COOR	toxic	$F(CH_2)_5COOR$	toxic
FCH_2CH_2COOR	non-toxic	$F(CH_2)_7COOR$	toxic
$F(CH_2)_3COOR$	toxic	$F(CH_2)_{10}COOR$	non-toxic
$F(CH_2)_4COOR$	non-toxic		

Other series of fluorine compounds showing a similar alternation in toxic properties are also known[59].

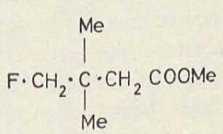
Knoop[60] suggested in 1906 that fatty acids were metabolized in the body with loss of two carbon atoms at a time by oxidation at the β-carbon atom[60].

$$RCH_2CH_2COOH \rightarrow R\cdot COOH + CH_3COOH$$

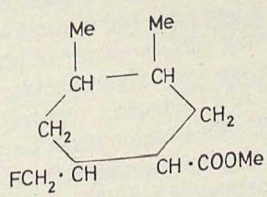
It will be readily seen in our series $F(CH_2)_nCOOH$, that when *n* is odd, β-oxidation yields toxic fluoroacetic acid, whereas when *n* is even, the compound will be oxidized only as far as the non-toxic β-fluoropropionic acid, FCH_2CH_2COOH. The results are in accord with this hypothesis and provide a proof of a kind not hitherto achieved of the process of β-oxidation in the living animal body.

It could be argued that further β-oxidation of β-fluoropropionic acid could yield fluoroformic acid, FCOOH. It has, however, been clearly demonstrated that ethyl fluoroformate, FCOOEt, is itself devoid of toxic properties. Therefore, in any case, the process of β-oxidation in the series $F(CH_2)_nCOOH$, where *n* is even, will ultimately give a non-toxic end-product.

If our theory of alternating toxicities is right, then blocking of the β-position to prevent oxidation should give a compound devoid of toxic properties[58, 61]. For this purpose ethyl 2,2-dimethyl-3-fluorobutyrate (XI) was synthesized, and shown to be indeed non-toxic. Another way of testing



(XI)



(XII)

$FCH_2CH_2CH_2COOMe$

(XIII)

Among many 'fluoroacetates' prepared in Cambridge, reference may be made to several of particular interest from the point of view of toxic action. *Fluoroaspirin* (fluoroacetyl salicylic acid) caused initial stupor without convulsions in mice. *Di-2-fluoroethyl phosphorofluoridate* was prepared with the idea of combining the 'toxic principles' of fluoroacetates and phosphorofluoridates. The compound caused myosis, but was less toxic than anticipated. At a concentration of 0·5 g/m^3 (10-minute exposure) it produced, however, in rats a remarkable state of hyperactivity followed by convulsions of an unusual type leading to coma and death.

Triethyllead fluoroacetate, $FCH_2COOPbEt_3$—A systematic study of the sternutatory properties (irritation of nose, throat and chest) of organolead salts has been made in Cambridge[65]. Triethyllead fluoroacetate is interesting in that it effectively combines the sternutatory properties of trialkyllead salts with the convulsant action of the fluoroacetates.

Sesqui-fluoro-H. 2,2′-Dichlorodiethyl ethylene dithioglycol (sesqui-H) is an outstandingly powerful vesicant. The fluorine analogue (XVII), often called 'sesqui-fluoro-H', has been prepared as follows[66]:

$$FCH_2CH_2Br + HSCH_2CH_2SH + BrCH_2CH_2F \xrightarrow{NaOH} FCH_2CH_2{\cdot}SCH_2CH_2S{\cdot}CH_2CH_2F$$

(XVII)

It proved to be a non-vesicant and furthermore it did not produce fluoroacetate-like symptoms in the animal body. This latter observation is to be expected as it is difficult to see how such a compound could be readily metabolized to fluoroacetic acid in the body.

Treatment of fluoroacetate poisoning

Vomiting should be induced when possible. Immediate and thorough gastric lavage is recommended. Although no very effective antidote has yet been found, for the reasons indicated above (page 202), large doses of glyceryl monoacetate should be administered by intravenous injection. Barbiturates may be helpful.

SOME FURTHER APPLICATIONS OF P—F AND C—F COMPOUNDS

In a secret patent in 1943 it was suggested that some of the above compounds might be useful as insecticides, fungicides and also be capable of clinical application[67]. All these expectations have been, in fact, realized.

The condition of post-operative paralytic ileus[68] (paralysis of peristaltic movement of the gut) appears to be relieved by intramuscular injection of D.F.P.[69] and other organophosphorus compounds. Transient relief of symptoms of myasthenia gravis (in which there may be too little acetylcholine or too much cholinesterase) has been recorded. D.F.P. has also been suggested for treatment of glaucoma by direct administration of an oily solution

to the affected eye. Glaucoma is caused by an increased intraocular pressure within the eyeball. It seems that D.F.P. facilitates the escape of the fluid of the aqueous humour through the canal of Schlemm[70].

As mentioned above, while work on organic compounds containing phosphorus and fluorine was proceeding in England during World War II, German workers pursued projects similar in some respects. Schrader suggested many compounds that might be useful as insecticides.

Toxic compounds that can be readily absorbed by a living plant through its roots or leaves are known as systemic insecticides[71]. Among such are organo-phosphorus compounds and also many compounds containing fluorine. Sodium fluoroacetate is a systemic insecticide[72], but in view of what we have said above it is doubtful whether this chemically stable compound should be used for this purpose. This warning applies to many C—F compounds.

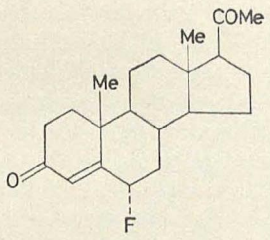
As previously stated (page 190) there is often a correlation between anticholinesterase activity *in vitro* and mammalian toxicity. This is not always so; for example, the toxicity of the phosphoramidate (V) is similar to that of D.F.P., whereas its anticholinesterase activity is low. This apparent anomaly is accounted for by the conversion of (V) in living tissue into a new oxidation product which is the real toxic material with marked esterase-inhibiting properties. Hence it has a delayed action. Several other 'inactive' phosphorus compounds are changed to toxic materials by animal and plant tissue—that is to say that the tissue is capable of lethal synthesis[73].

Intraperitoneal injection of very small doses of sodium fluoroacetate inhibits the growth of influenza virus in the lungs of mice and also of the poliomyelitis virus in the brain of mice, but whether beneficial results are likely to accrue with human beings is not established.

RECENT WORK ON COMPOUNDS CONTAINING THE C—F LINK

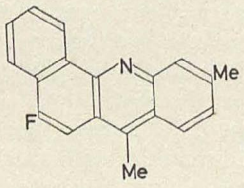
Some very recent work by investigators in Liége is of considerable interest[74]. It is known that cells are damaged by X-rays and γ-rays. It appears that the deoxyribonucleic acid of the cell nucleus is destroyed (following radiation) by the enzyme deoxyribonuclease which occurs in mitochondria. This reaction requires Mg^{++} ions. The Belgian workers have established that previous injections of sodium fluoroacetate into mice give some protection against irradiation. This may be due to the fact that the fluoroacetate causes citric acid to accumulate in the mitochondria, and that the citrate then combines with and so removes the Mg^{++} ions.

Though not toxic in the strict sense of the term, certain compounds have greatly altered physiological action when hydrogen is replaced by fluorine. In this connexion, American workers[75] have reported that synthetic mono-fluoro-derivatives of steroid hormones are far more potent than the parent substances. Thus 6-α-fluoroprogesterone (XVIII) is ten times as active as progesterone itself. 6-α-Fluorohydrocortisone acetate has 11 times the glucocortisoid activity of hydrocortisone. Why the replacement of hydrogen by fluorine should give this increased hormonal activity in this way is not exactly known.

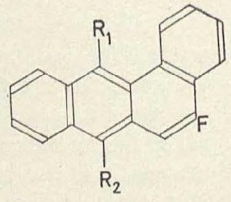


(XVIII)

Bergmann and his colleagues[76] have synthesized fluoro-derivatives of polycyclic carcinogenic compounds (e.g. XIX, XX):



(XIX)

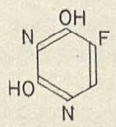


(XX)

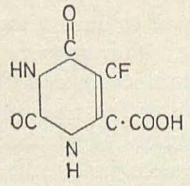
The biological activity of such compounds has not yet been reported, but is awaited with interest.

Newman and Galt[77] have synthesized 3′-fluoro- and 4-fluoro-10-methyl—1,2-benzanthracenes with a view to producing carcinogenic activity. Another compound which has been synthesized 'to investigate its carcinogenicity' is 2-fluoro-5-acetylaminofluorene[78].

A considerable amount of work is currently appearing on C—F compounds. Among interesting applications the following should be noted. 5-Fluorouracil (XXI) and related compounds inhibit mammalian tumours by interfering, in a complex manner, with both ribonucleic acid and deoxyribose nucleic acid[79]. 5-Fluorouracil and fluoroorotic acid (XXII) are active bacteriostatic agents[80].



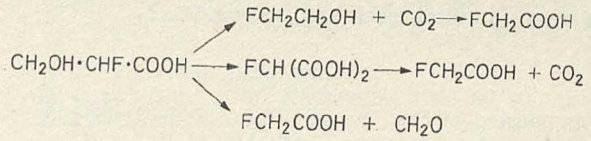
(XXI)



(XXII)

DL-1-deoxy-1-fluoroglycerol is toxic. Death is associated with convulsions, bradycardia and accumulation of citrate, thus indicating metabolism via fluoroacetate[81]. 2-Deoxy-2-fluoroglyceric acid (XXIII) is also toxic and gives rise to citrate accumulation. The conversion of the fluoroglyceric acid is not simple: three routes have been suggested[82]. The first route has been

eliminated since it has been shown that fluoroglyceric acid is toxic to kidney mitochondria whereas fluoroethanol is not. If the second route is followed then fluoromalonic acid should be toxic. The present indications are that fluoromalonic acid is in fact non-toxic. If this is confirmed then a metabolic path as suggested by the third route must be considered[83].



(XXIII)

FLUORINATED HYDROCARBONS

In general fluorinated hydrocarbons (fluorocarbons) are non-toxic. They do not, of course, contain the essential FCH_2CO- group. Furthermore fluorinated hydrocarbons are less toxic than the corresponding chlorohydrocarbons[84]. The concentrations of vapours of certain related hydrocarbons required to kill guinea-pigs during a 10-minute exposure are as follows: 7 per cent for $CHCl_3$, 21 per cent for $CHCl_2F$ and 63 per cent for $CHClF_2$, so that the introduction of each F atom in place of a Cl atom lowers the toxicity by a third. Fluothane, $CF_3 \cdot CHClBr$ is a non-irritant sweet-smelling liquid, b.p. 50·2°, and is a promising anaesthetic[85]. It forms non-explosive and non-inflammable mixtures with oxygen or nitrous oxide. Furthermore it is non-toxic. The induction period is rapid and the after-effects are negligible.

The refrigerant 'freon', CCl_2F_2, has a very low toxicity. Inhalation of such a high concentration as 20 per cent does not even produce unconsciousness, although analgesia and confusion result. Recovery is complete within 10 minutes.

In general the perfluoroalkanes, C_nF_{2n+2}, are chemically inert and are non-toxic. Certain members of the series are used as high temperature lubricants. Fluorinated alkenes do, however, exhibit toxic properties, although their mode of action is not that of the fluoroacetates. Thus perfluoroisobutylene, $(CF_3)_2C = CF_2$, is a dangerous substance[86].

The polymer Teflon $[(CF_2CF_2)_n$, polytetrafluoroethylene] is non-toxic. When, however, it is heated to 500–800° it gives toxic decomposition products[87] containing hydrogen fluoride and fluorocarbons including perfluoroisobutylene. The symptoms from hot Teflon fumes are coughing, tightness of the chest, dyspnoea and convulsions in severe cases.

CONCLUSION

Toxic organic compounds containing fluorine were made originally as potential chemical warfare agents[88]. Fortunately they were not used for that purpose. In this chapter an attempt has been made to explain the uses to which some of these compounds have been put and the applications

provide a striking example of the beating of the proverbial swords into ploughshares. Much has been revealed and clarified, but a great deal remains to be done: how, for example, can certain plants utilize inorganic fluoride in the synthesis of fluoroacetate; can other forms of life do this; is there more to be learnt about the fluoridation of water supplies; and how far will the study of appropriate organo-fluorine compounds reveal the mechanisms of certain vital biological mechanisms?

REFERENCES

[1] Paley, A. and Seifter, J. *Proc. Soc. Exp. Biol. N.Y.* 1941, **46**, 190
[2] McClure, F. J. *J. Amer. Med. Assoc.* 1949, **134**, 711
[3] Saunders, B. C. and Stark, B. P. *Tetrahedron*, 1958, **4**, 769
[4] Lindbeck, W. L., Hill, I. B. and Beeman, J. A. *J. Amer. Med. Assoc.* 1943, **121**, 826
[5] Fullerton, W. W. *New England J. Med.* 1930, **203**, 423
[6] Editorial. *Pharm. J.* 1952, **168**, 22
[7] Rabinowitch, I. M. *Canad. Med. Assoc. J.* 1945, **52**, 345
[8] von Oettingen, W. F. *Poisoning. A Guide to Clinical Diagnosis and Treatment.* 2nd Ed. p. 364. 1958. Philadelphia, London; W. B. Saunders.
[9] DeEds, F. *J. Amer. Dent. Assoc.* 1936, **23**, 568
[10] Garner, R. J. *Veterinary Toxicology.* 1st Ed. p. 79, 1957. London; Baillière, Tindall and Cox
[11] Churchill, H. *J. Ind. Eng. Chem.* 1931, **23**, 996
[12] Forrest, J. *Chem. and Ind.* 1957, 64
[13] Steyn, D. G. *The Problem of Dental Caries.* 1st Ed. p. 47, 1958. Johannesburg; Voortrekkerpers
[14] Ockerse, T. and Wasserstein, B. *J. Amer. Dent. Assoc.*, 1955, **50**, 536
[15] Steyn, D. G. *The Problem of Dental Caries.* 1st Ed. p. 177, 1958. Johannesburg; Voortrekkerpers
[16] World Health Organization. *Expert Committee on Water Fluoridation.* 1st Report, 1958. Tech. Rep. Series No. 146
[17] Saunders, B. C. Ministry of Supply Meeting, London, December, 1951; McCombie, H. and Saunders, B. C. *Nature*, 1946, **157**, 287. [This gives dates of Reports to Ministry of Supply, London, 1941 onwards]; Saunders, B. C. and Stacey, G. J. *J. Chem. Soc.* 1948, 695
[18] Cook, H. G., Saunders, B. C. and Smith, F. E. *J. Chem. Soc.* 1949, 635
[19] Saunders, B. C., Stacey, G. J., Wild, F. and Wilding, I. G. E. *J. Chem. Soc.* 1948, 695
[20] Adrian, E. D., Feldberg, W. and Kilby, B. A. *Brit. J. Pharmacol.* 1947, **2**, 56; Mackworth, J. F. and Webb, E. C. *Biochem. J.* 1948, **42**, 191
[21] Aldridge, W. N. 'Organo Phosphorus Compounds', *Rep. Chem. Soc.*, 1956, 214
[22] Saunders, B. C. and Worthy, T. S. *J. Chem. Soc.* 150, 1320
[23] Boursnell, J. C. and Webb, E. C. *Nature*, 1949, **164**, 875
[24] Saunders, B. C. and Stacey, G. J. *J. Chem. Soc.* 1948, 695
[25] McCombie, H., Saunders, B. C. and Wheeler, C. C. B.P. 601, 210 (April 30, 1948)
[26] Chapman, N. B. and Saunders, B. C. *J. Chem. Soc.* 1948, 1010; McCombie, H., Saunders, B. C., Chapman, N. B., Heap, R. and Pratt, J. D. B.P. 602, 446
[27] Heap, R. and Saunders, B. C. *J. Chem. Soc.* 1948, 1313
[28] McCombie, H. and Saunders, B. C. *Nature*, 1946, **157**, 776
[29] Schrader, G. *B.I.O.S. Final Report*, 1947
[30] Dale, Sir Henry, *Endeavour*, 1953, **12**, 117
[31] Saunders, B. C. *Some Aspects of the Chemistry and Toxic Action of Organic Compounds containing Phosphorus and Fluorine*, p. 34, 1957. London; Cambridge University Press
[32] Saunders, B. C. 'Physiological Action of Diisopropyl Phosphorofluoridate'. *Chem. Soc.* London, 1957, p. 165. Special Publication, No. 8
[33] Saunders, B. C. *Endeavour*, 1960, **19**, 37
[34] Wilson, I. B. *Chem. and Eng. News*, 1955, **33**, 136

[35] Berry, W. K., Davies, D. R. and Green, A. L. *Biochem. J.*, 1959, **71**, 15P
[36] Hobbiger, F. *Nature*, 1958, **182**, 1498
[37] Hobbiger, F. *Nature*, 1958, **182**, 1672
[38] Swarts, F. *Bull. Acad. roy. Belg.* 1896, **31**, 675
[39] McCombie, H. and Saunders, B. C. *Nature*, 1946, **158**, 382 [This gives dates of Reports to Ministry of Supply, London, 1942 onwards]; Saunders, B. C. and Stacey, G. J. *J. Chem. Soc.* 1948, 1773
[40] Bucke, F. J., Heap, R. and Saunders, B. C. *J. Chem. Soc.*, 1949, 912
[41] Saunders, B. C., Stacey, G. J. and Wilding, I. G. E. *J. Chem. Soc.* 1949, 773
[42] Saunders, B. C. *J. Chem. Soc.* 1949, 1279
[43] Chenoweth, M. B. *J. Pharmacol.* 1949, **97**, 383
[44] Chenoweth, M. B. and Gilman, A. *J. Pharmacol.* 1946, **87**, 90
[45] Harrison, J. W. E., Ambrus, J. L., Ambrus, C. H., Rees, E. W., Peters, R. H., Reece, L. C. and Baker, T. *J. Amer. Med. Assoc.* 1952, **149**, 1520
[46] Bartlett, J. R. and Guzman-Barron, E. S. *J. Biol. Chem.* 1947, **170**, 67
[47] Frick, E. J. and Boebel, F. W. *Vet. Med.* 1946, **41**, 196
[48] Annison, E. F., Hill, K. J., Lindsay, D. B. and Peters, R. A. *J. Comp. Path.* 1960, **70**, 145
[49] Mirosevic-Sorgo, P. and Saunders, B. C. *Tetrahedron*, 1959, **5**, 38
[50] Bronnert, D. L. E. and Saunders, B. C. *Tetrahedron*, 1960. In the press
[51] Marais, J. S. C. Onderstepoort. *J. Vet. Sci. An.* 1943, **18**, 203; 1944, **20**, 67
[52] Steyn, D. G. *Fmg in S. Afr.* July, 1939
[53] LeRougetel, Sir J. Correspondence with Saunders, B. C. December, 1953
[54] Renner, W. *Brit. Med. J.* 1904, **1**, 1314
[55] Peters, Sir R. A. and Hall, R. J. *Biochem. Pharmacol.* 1959, **2**, 25; *Nature*, 1960, **187**, 573
[56] Saunders, B. C. *Peroxidase. Action and Use in Organic Synthesis.* Lecture to Royal Institute of Chemistry, 1957, No. 1
[57] Hughes, G. M. K. and Saunders, B. C. *J. Chem. Soc.* 1954, 4630
[58] Saunders, B. C. *Nature*, 1947, **160**, 179
[59] Pattison, F. L. M. *Toxic Aliphatic Fluorine Compounds*, 1st Ed. p. 113, 1959. London; Elsevier Press
[60] Knoop, F. *Beitr. Chem. Physiol. Path.* 1906, **11**, 411
[61] Pattison, F. L. M. and Saunders, B. C. *J. Chem. Soc.* 1949, 2745
[62] Peters, Sir R. A. Croonian Lecture. *Proc. Roy. Soc., B*, 1952, **139**, 143; *Endeavour*, 1954, **13**, 147; *Advances in Enzymology*, 1957, **XVIII**, 113
[63] Chenoweth, M. B., Kandel, A., Johnson, L. B. and Bennett, D. R. *J. Pharmacol. Exp. Therap.* 1951, **102**, 31
[64] Avi-Dor, Y. and Mager, J. *Biochem. J.* 1956, **63**, 613
[65] McCombie, H. and Saunders, B. C. *Nature*, 1949, **159**, 491; Saunders, B. C. and Stacey, G. J. *J. Chem. Soc.* 1949, 919
[66] Saunders, B. C. and Stacey, G. J. *J. Chem. Soc.* 1949, p. 916
[67] Saunders, B. C. *et al.* B.P. 602, 446
[68] Whitby, Sir L. *Practitioner*, 1947, **159**, 243
[69] Quilliam, J. P. and Quilliam, J. A. *Med. Pr.* 1947, Oct. 22
[70] See Reference 31, p. 195
[71] Martin, H. *Ann. Appl. Biol.* 1949, **36**, 153
[72] David, W. A. L. *Nature*, 1950, **165**, 493
[73] Hartley, G. S. 15*th Int. Cong. Pure Appl. chem.* New York, 1951; see also Spencer, E. Y. *Phosphoric Esters and Related Compounds, Chem. Soc., London*, 1957, p. 171. Special Publication No. 8
[74] Bacq, Z. M., Fischer, P., Herve, A., Liebecq, C. and Liebecq-Hutter, S. *Nature*, 1958, **182**, 175
[75] Hogg, J. A., Spero, G. B., Thompson, J. L., Magerlein, B. J., Schneider, W. P., Peterson, D. H., Sebek, O. K., Murray, H. C., Babcock, J. C., Pederson, R. L. and Campbell, J. H. *Chem. and Ind.* 1958, 1002
[76] Bergmann, E. D., Blum, J., Butano, S. and Heller, A. *Tetrahedron Letters*, 1959, **1**, 15
[77] Newman, M. S. and Galt, R. H. B. *J. Org. Chem.* 1960, **25**, 214
[78] Dahlgard, M., Bokil, I. D. and Ray, F. E. *J. Org. Chem.* 1960, **25**, 951

[79] Harbers, E. and Heidelberger, C. *Abs. Int. Congr. Biochem.* 1958, 4th Meeting Vienna
[80] Heidelberger, C., Chaudhuri, N. K., Danneberg, P., Moorer, D., Griesbach, L., Duschinsky, R., Schnitzer, R. J., Pleven, E. and Scheiner, J. M. *Nature*, 1957, **179**, 663; Scheiner, J. M., Kostelak, E. and Duschinsky, R. *Fed. Proc.* 1957, **16**, 202
[81] O'Brien, R. D. and Peters, R. A. *Biochem. J.* 1958, **70**, 188
[82] Peters, R. A. and Treble, D. H. Private communication, 1960
[83] Bronnert, D. L. E. and Saunders, B. C. Work in progress, 1960
[84] Sollmann, T. *Pharmacology*, p. 923, 8th Ed. Philadelphia; Saunders
[85] Raventos, J. *Brit. J. Pharmacol.* 1956, **11**, 394; Suckling, C. W. *Brit. J. Anaesth.* 1957, **29**, 466
[86] Brice, T. J., La Zerte, J. D., Hals, L. J. and Pearlson, W. H. *J. Amer. Chem. Soc.* 1953, **75**, 2698
[87] Treon, J. F., Cappel, J. W., Cleveland, F. P., Larson, E. E., Atchley, R. W. and Denham, R. I. *Amer. Ind. Hyg. Assoc. Quart.* 1955, **16**, 187
[88] Saunders, B. C. *Chemistry and Toxicology of Organic Fluorine and Phosphorus Compounds.* Lecture given to the Royal Institute of Chemistry, 1953, No. 1

INDEX

This index is intended to supplement the lists of contents to be found at the beginning of each article