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TOXICITY AND ENZYMES*

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Toxicity of substances may often be explained by their influence on enzymes. The increasing knowledge of the reaction and properties of enzymes and also of their distribution in living tissues has presented many ways in which toxic substances may act. Some of these possibilites have been discussed in this paper.

In this paper I shall confine my remarks to various aspects of toxicity to mammals and their enzymes. The examples I use to illustrate various points are selected for the most part from work with which my colleagues and I have been associated. This does not imply that these have any special virtue of their own but is rather due to my lack of knowledge. The examples themselves will sometimes be of interest from a practical point of view but more often will appear to be of theoretical and academic interest only. I believe, however, there is and should be no division between these two aspects; an intelligent answer or opinion on many practical question of toxicology can often only be given when there is a background of theoretical knowledge of their action in biochemical and physiological terms.

Toxicity is not a term with one unambiguous meaning. There is, however, a prevalent view that toxicity is a precise entity and rather like a physical constant such as boiling point or solubility. Even the relatively straightforward acute toxicity of a substance must be qualified by many variables of which species and route of administration are examples. Such a value, even if defined, is of little use for the interpretation of hazard if other information such as the persistance of the substance in the organism is not available. To attempt to evaluate the dangers to man of chronic exposure to a substance such as insecticide from a simple toxicity test on rats is rather like expecting to learn a language by opening a dictionary on one page only.

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From a practical point of view it might be thought that the toxicity of non-volatile material would be best studied by oral administration. This is probably the most usual route of intoxication, but I am sure that our views of the danger of the use of a substance would be much modified, if, although it proved almost non-toxic by mouth, it proved to be highly toxic by intravenous injection. Such proved to be the case with beryllium which was our first problem when we formed our toxicology unit. It had been concluded from an extensive review of the literature (1) that beryllium was non-toxic. These writers failed to emphasize the importance of earlier work by Siem (2) and Comar (3). Our work (4) immediately showed that beryllium sulphate or any salt of beryllium was highly toxic when injected intravenously – L. D. 50 0.5–1 mg/Kilo to rabbits, rats and mice. The toxicity of beryllium administered orally is very low but when larger quantities are given another mode of toxicity for beryllium is found. Branno, Kay & Guyatt (5) showed that feeding beryllium to rats will produce rickets by depriving animals of phosphate and these animals die of gross phosphate deficiency. Incidentally, it is the extreme insolubility of beryllium phosphate which makes work *in vitro* on isolated biological systems so difficult technically. Another example may be taken of some work which Dr. Vandekar and Dr. Heath carried out a year or so ago. Here it was found that organo-phosphorus compounds of the systox type are methylated upon storage to give sulphonium compounds such as 00 dimethyl S – ethyl sulphonio ethyl methyl phosphorothioalate (6, 7 & 8). The oral toxicity of these compounds is at least 100–200 times lower than that upon intravenous injection. This is probably due to poor absorption from the gut and is associated with the positive charge on the sulphur atom. In this connection the extensive work by Brodie and co-workers upon the absorption of ionised compounds through cell membranes is of much interest (9, 10).

It is essential therefore to have a measure of the intrinsic toxicity of a compound and this is usually regarded as its toxicity by intravenous injection. It can be assumed that if a compound is not toxic by intravenous injection, then it will be safe to use as far as acute hazards are concerned. Even intravenous injection however is not without its difficulties with many compounds which are insoluble in water.

Enzymes are an essential part of living matter and it is becoming increasingly held that toxic substances act by interfering with the action of enzymes and the term „biochemical lesion" is being widely used to indicate that pathological disturbances in tissues may be initiated by changes in their biochemistry (11). The action of enzymes must now be treated in a very broad way for in addition to the action of toxic substances upon enzymes so that their action is prevented, there are many ways that the lack of specificity of enzymes may be used so that a nonphysiological metabolite is formed. Much has been said about specific catalysis (12) and there is no doubt that in the living organism this is so but the organic chemists have produced a new

situation where very small modifications to a molecule may be made and the enzymes often cannot „recognize" this altered substrate from its physiological substrate. In this way a metabolite is transformed and continues along usual pathways until it reaches an enzyme which rejects it. It is not enough realized that enzymes are specific relative to the substrates they are normally presented with – for example, succinic dehydrogenase can distinguish between succinic and malic acids. However, such are the potentialities of organic chemists that many unphysiological modifications may be made which will completely mislead the enzyme. A good example of this is the fact that true cholinesterase of the central nervous system hydrolyses acetylthiocholine at a higher rate than acetylcholine (13). Nevertheless this does not alter the fact that acetylcholine is its natural substrate.

The concept of a „biochemical lesion" leading to pathological changes has become of major importance now that the gap between enzymes and structure is beginning to close. The concept of an inert structure to cells is slowly giving way to the realisation that enzymes make up a very large proportion of the cell protein (14). Although an ordered metabolism depends upon organised structures the structure itself is probably made up almost entirely of enzymes themselves. This is becoming particularly apparent with such highly organised structures as the mitochondria and here also the concept is slowly emerging of the possibility of structural alterations being involved in some hormonal controls of metabolism (15, 16, 17).

Of course, although enzymes are a vital constituent of living matter not all enzymes are of the same importance for the maintenance of life. Although it seems clear that true cholinesterase of the central nervous system is an essential enzyme, pseudo cholinesterase has no known function and may be drastically reduced with no untoward effects upon the animals (18). The same appears to be true for many of the esterases present in the intestine and liver (19). These may be reduced to very low levels in rats by the administration of tri *o* cresyl phosphate with no apparent clinical effects (20). This raises a fine point for the toxicologist whether the inhibition of the pseudocholinesterase of human blood should be regarded as a manifestation of toxicity or purely an indication of absorption of the organophosphorus compound and of no importance from the point of view of danger to health.

These enzymes which we have been discussing are hydrolytic enzymes. The enzymes involving oxidative processes upon which the life of the animal obviously depends are vital targets for toxic substances. For instance cytochrome oxidase is one such enzyme – all the electron transport involved in the oxidation of substrates is channelled through this enzyme and its inhibition will produce profound effects. Cyanide is well known as an inhibitor of this enzyme (21) but now would not be regarded as a very potent one.

Although many enzymes such ascytochrome oxidase and true cholinesterase are essential for the life of the animal there are differences

in the amount of enzyme there is in excess of normal requirements. Although true cholinesterase is an essential enzyme there does seem to be a large excess over that required for normal function. For instance, 95% of the true cholinesterase of the central nervous system can be inhibited before noticeable symptoms appear. However, when we enter the field of regulation of cell metabolism it becomes clear that certain reactions are „pace maker reaction" (22) and govern the overall speed of whole systems of enzymes such as glycolysis and mitochondrial oxidations (23). These are clearly vital steps and their inhibition will produce profound effects.

The preceding discussion will I hope have made it clear that the modification of the action of enzymes is an important way toxic substances exert their action. However, enzymes vary in their importance for the economy of the animal and it is possible to inhibit many enzymes *in vivo* and produce no detectable clinical effect.

Now we should deal with different modes of inhibition. The inhibition of cytochrome oxidase by cyanide is by the formation of a cyanide complex with the cytochrome which has a finite dissociation complex. In other words, if some substance could be added to the system which would remove cyanide then the complex would dissociate. This has been put to a practical test by Sörbo (24) who has shown that if the enzyme rhodanase is injected with sodium thiosulphate animals can survive several lethal doses of cyanide. This, I believe, is the first time that an enzyme has been used for the treatment of a condition produced by a toxic substance. The inhibition by cyanide is therefore reversible and the enzymic activity can be returned *in vitro* by dialysis of the inhibited enzyme. Inhibition of enzymes by mercurials and their reversal by glutathione (25 & 26) and the inhibition of α-Ketoacid oxidases by arsenite or phenylarsenious acid and their reversal by BAL (27) are examples of this type. On the other hand some inhibitions are due to the formation of covalent bonds with the enzyme and these are correspondingly more difficult to reverse. The best example of this type of inhibition is the action of the organophosphorus compounds. I shall be talking of this in my next lecture but perhaps I might mention a few consequences of this action. Since stable covalent bonds are formed the phosphorylated enzyme must be chemically regenerated by hydrolysis (28) or by reactivation by some of the now well known reactivators (29). The inhibited enzyme is so stable that in several instances the rate of return of cholinesterase in erythrocytes has been taken as the rate of formation of red cells (30) and in many instances it is a reasonable view that return of enzyme activity is due to resynthesis of the enzyme. The difference between this type of inhibition and the former with SH groups is that there is no finite dissociation and so the inhibition is much more permanent. Prolonged dialysis by itself will not remove the dialkyl phosphate from the enzyme whereas prolonged dialysis of SH – mercurial complexes although slow will cause some reactivation. This has the effect of

making animals much more sensitive to second doses of organo-phosphorus compounds. Other reactions of inhibitions with enzymes of a similar type as the organo-phosphorus compounds are iodo acetate with SH enzymes and recently some of the substituted hydrazines with enzymes requiring pyridoxal phosphate as a coenzyme (31, 32).

The distribution of a toxic substance influences the type of effect which is obtained. Returning to beryllium, the only pathological damage of any note after the intravenous injection of beryllium sulphate (4) is to the liver. Why is the liver singled out? Is it due to there being a single enzyme in the liver which is sensitive to beryllium and which is not present in other tissues or is beryllium only presented to the liver in high enough concentration? Early in this work it became apparent that beryllium was concentrated in the liver far more than in other organs (33). A method for the determination of beryllium was elaborated (34) and using the dye used in this method a histochemical method for the localisation of beryllium in sections of tissue was worked out (35). Recently, Cheng (36) has shown that essentially the process is that beryllium sulphate forms in the blood streamberyllium phosphate in a colloidal state. These particles are taken from the blood stream into the Kupffer cells of the liver and from these particles of beryllium phosphate beryllium slowly diffuses out to the rest of the liver causing necrosis of the liver. The enzymic mechanism whereby this takes place has not yet been worked out though perhaps a clue is that beryllium inhibits alkaline phosphatase and that the inhibition is less when the magnesium concentration is increased (37). It is not suggested that the inhibition of alkaline phosphatase is the cause of the death of the liver cell but that possibly beryllium is replacing magnesium essential to another enzyme.

In some instances the availability of a method for estimation of a substance produces many difficulties in interpretation. Such a case is the toxicity of triethyltin. The only pathological symptom produced by this substance is an interstitial oedema of the white matter (38). No damage was produced in any other tissues and it was tempting to conclude, particularly since triethyltin at neutral pH is soluble in organic solvents, that the triethyltin was concentrated into the lipoidal material of the brain. However, using a method for the determination of the intact triethyltin molecule (39) it quickly became clear that this was not the case. In the rat a high concentration was found in the erythrocytes, and was also present in the liver and brain. The concentration in the brain was less than the liver (40). Other work demonstrated that the respiration of slices prepared from brain of animals intoxicated by triethyltin was lowered while those from liver were unaffected (40). This seemed to fit well with the facts in the whole animal but is has now shown that the temperature of the liver is down and there are changes in the nucleotide concentrations in this tissue (41). What is even more puzzling is that it has been shown that brain and liver mitochondria are equally sensitive to triethyltin *in vitro* (42).

We are left with the possibility that the brain is much more sensitive to certain kinds of inhibition. One thing is certain that when we understand the toxicology of triethyltin we shall know much more physiology and biochemistry of the whole animal.

Examination of some new organo-phosphorus compounds has raised questions about their precise mode of action *in vivo*. It has long been known that animals die after Schradan with little or no inhibition of their brain cholinesterase (43). It has recently been shown by using these sulphonium compounds, and compounds containing ionised quaternary groups, that here again although they are highly toxic (7) brain cholinesterase is not inhibited. This result is probably a reflection of the difficulty of compounds with positively charged quaternary groups have in passing the blood brain barrier. However, it also poses some problems to the physiologist as to the relative role of inhibition of cholinesterase in the central nervous system and the peripheral myoneural junctions.

Since the use of centrifugation for the separation of particulates from cells it is becoming clear that there are many further compartments inside the cell. The mitochondrion is one but many other substances are being found in particles. For example, adrenaline (44) and acetylcholine (45). It is clear that the detailed distribution of toxic substances is of vital interest to an understanding of their mode of action. Other kinds of metabolic compartments are also at the moment being discussed with reference to the regulation of cell metabolism (23).

Until relatively recently it was thought that most substances which were toxic were toxic themselves and it had not been appreciated that organisms would convert non-toxic substances to lethal substances. This process has been called „lethal synthesis" (46) though I think it is clear that this is not any purposeful conversion by the organism. Although some form of teleology is justified when considering the living organism and the processes which normally take place within them (47) it seems certain that when organisms are presented with entirely new organic molecules the enzymes of the organism will deal with them if they are sufficiently similar to their normal substrates. In this sense there probably is no difference in principle in the processes of detoxification and lethal synthesis. What has now become the classical work of Peters and co-workes (46), on the mechanism whereby fluoroacetate becomes toxic, is well known. All enzyme systems *in vitro* are unafected by fluoroacetate but this is treated as acetate would be and fluorocitric acid synthesised from it. This fluorocitric acid cannot be utilised by aconitase and inhibits this enzyme so causing the normal metabolisms to be prevented and a concentration of citric acid to be built up.

The preceding example was a process whereby enzymes effect this conversion. Cyanogen chloride is a very toxic substance with about half the toxicity of hydrocyanic acid (48). It has been shown that the physiological responses to cyanogen chloride and hydrogen cyanide are

identical (48) and it was shown, after the development of a very sensitive method of the determination of cyanide and thiocyanate (49) that cyanogen chloride is converted to cyanide *in vivo* and that this conversion can explain entirely its toxicity (48). Further work has shown that this conversion is not an enzymic process in the usual sense for after a very fast reaction of cyanogen chloride with haemoglobin hydrocyanic acid is liberated (50). This reaction occurs with compounds with vicinal sulphydryl and amino groups (50) and it is presumed that these groups are involved in native haemoglobin. This process appears to be a pure chemical reaction.

If the liver cell is disrupted and fractionated by centrifugation at different speeds into different size particles it is found that the microsomal fraction which is sedimented at the highest speeds (100,000 g) can modify a variety of very dissimilar substances: oxidation of side chains of barbiturates (51), dealkylation of amidopyrine (52), deamination of amphetamine (53) cleavage of the ether bridge of phenacetin (54) and hydroxylation of aniline (55). All of these reactions can be considered detoxifications. However, in recent years, many instances of lethal synthesis have been found which are carried out by this system in microsomes: Conversion of many inactive organo-phosphorus compounds to active inhibitors of cholinesterase (parathion (00-diethyl 0-*p*-nitrophenyl phosphorothionate); schraden (octamethy pyrophosphoramide): (56) dimefox (57) (NN bis dimethyl phosphoro diamdic fluoride) malathion (58) (00-dimethyl-S-(1, 2-dicarboethoxyethyl) phosphorodithioate) as examples, and the metabolism of dimethyl nitrosamine (59), and recently, the conversion of the inactive tetraethyltin and tetraethyl lead to the active compounds triethyltin and triethyllead (60, 61).

The only example I wish to discuss is one which involves both detoxification and lethal synthesis and also is concerned with what has come to be known as potentiation, an important aspect of insecticide toxicology. Malathion is relatively non-toxic orally to rats (1 gm/Kg) and this is presumably because the intestine and liver contain large amounts of esterases (19) which hydrolyse the ethyl succinate end of the molecule. This prevents the conversion of the compound into an active compound by oxidation of the thionosulphur. However, if the animal has been previously treated with EPN (Ethyl-p-nitrophenyl thionobenzenephosphonate) or many other organo-phosphorus compounds which inhibit the esterases of the gut and liver the intact malathion molecule reaches the microsomal system of the liver cell, is oxidised to its oxygen analogue, maloxon and becomes much more toxic (62). Tri *o* cresylphosphate given to rats in doses of 100 mg/Kilo is converted by the liver (64) to a compound which inhibits the esterases. The toxicity of malathion to rats before and after this treatment is 1100 mg/Kilo and 8 mg/Kilo respectively (63).

I am sure these examples will have convinced you that toxicity is a multivalent property which requires much knowledge of basic science for its understanding. Often the mechanism of action of toxic substances cannot be explained with the existing knowledge of biochemistry and physiology and many new techniques need to be elaborated in order to solve these problems. Indeed it is often by the use of toxic substances that new fields of biochemistry and physiology are uncovered. I hope to show you in my next two lectures how the use of toxic substances is teaching us more new biochemistry.

I would like to close with a quotation from Claude Bernard (65) »Poisons can be employed as means for the destruction of life or as agents for the treatment of the sick, but in addition to these two well recognised uses there is a third of particular interest to the physiologist. For him the poison becomes an instrument which dissociates and analyses the most delicate phenomena of living structures and by attending carefully to their mechanism in causing death, he can learn indirectly much about the physiological processes of life. Such is the way in which I have long regarded the action of toxic substances«.

References

1. *Hyslop, F., Palmes, E. D., Alford, W. C., Monaco, A. B., Fairhall, L. T.:* Nat. Inst. Hlth. Bull. No. 181 (1843).
2. *Siem, P.:* Inaug-Diss. Dorpat (1886).
3. *Comar, M.:* These Med. Paris (1935).
4. *Aldridge, W. N., Barnes, J. M., Denz, F. A.:* Experimental beryllium poisoning, Brit. J. exp. Path., 30 (1949) 375–389.
5. *Branion, H. D., Guyatt, B. L., Kay, H. D.:* Beryllium rickets, J. biol. Chem., 92 (1931) XI.
6. *Heath, D. F., Vandekar, M.:* Some spontaneous reactions of 00-dimenthyl S-ethylthioethyl phosphorothiolate and related compounds in water and on storage, and their effects on the toxicological properties of the compounds, Biochem. J., 67 (1957) 187–201.
7. *Vandekar, M., Heath, D. F.:* The reactivation of cholinesterase after inhibition *in vivo* by some dimethyl phosphate esters, Biochem. J., 67 (1957) 202–208.
8. *Heath, D .F.:* Reactions of ethylthioethyl 00-dimenthyl phosphorothiolates in water, J. Chem. Soc., (1958) 1643–1651.
9. *Brodie, B. B.:* Pathways of drug metabolism, J. Pharm. & Pharmacol., 8 (1956) 1–17.
10. *Brodie, B. B.; Hogben, C. A. M.:* Some physico-chemical factores in drug action, J. Pharm. & Pharmacol., 9 (1957) 345–380.
11. *Patons, B. A.:* Lancet, 1 (1936) 1161.
12. *Hopkins, F. G.:* Some aspects of biochemistry. The organising capacity of specific catalysts, Hopkins and Biochemistry. Heffer & Son. Cambridge 1949., (1932) 225–241.

13. *Koelle, G. B.:* The histochemical differentiation of types of cholinesterases and their localizations in tissues of the cat, J. Pharmacol., 100 (1950) 158–179.
14. *Dixon, M.:* Multi-enzymes systems, University Press, Cambridge, (1949).
15. *Maley, G. F., Lardy, H. A.:* Efficiency of phosphorylation in selected oxidations by mitochondria from normal and thyrotoxic rat livers, J. biol. Chem., 215 (1955) 377–388.
16. *Hoch, F. L., Lipmann, F.:* The uncoupling of respiration and phosphorylation by thyroid hormones, Proc. Nat. Acad. Sci. (NY), 40 (1954) 909–921.
17. *Lehninger, A. L., Ray, B. L., Schneider, M.:* The swelling of rat liver mitochondria by thyroxine and its reversal, J. Biophys. & Biochem. Cytol., 5 (1959) 97–108.
18. *Hawkins, R. D., Gunter, J. M.:* Studies on cholinesterase. 5. The selective inhibition of pseudo cholinesterase *in vivo*, Biochem. J., 40 (1946) 192–197.
19. *Aldridge, W. N.:* Some esterases of the rat. Biochem. J., 57 (1954) 692–702.
20. *Myers, D. K., Mendel, B.:* Studies on ali-esterases and other lipid-hydrolysing enzymes. I. Inhibition of the esterases and acetoacetate production of liver, Biochem. J., 53 (1953) 16–25.
21. *Keilin, D.:* Cytochrome and intracellular oxidase, Proc. Roy. Soc. s. B., 106 (1930) 418–444.
22. *Krebs, H. A.:* Control of metabolic processes, Endeavour, 16 (1957) 125–132.
23. *Ciba Symposium:* Regulation of cell metabolism, J. A. Churchill, London, (1959).
24. *Clemedson, C. J., Son Hultman, H. I., Sörbo, B.:* A combination of rhodanase and ethanethiosulfonate as an antidote in experimental cyanide poisoning, Acta. Physiol. Scand., 35 (1955) 31–35.
25. *Hellerman, L.:* Reversible inactivations of certain hydrolytic enzymes, Physiol. Revs., 17 (1937) 454–484.
26. *Barron, E. S. G., Singer, T. P.:* Studies on biological oxidations. XIX. Sulfhydryl enzymes in carbohydrate metabolism, J. biol. Chem., 157 (1945) 221–240.
27. *Aldridge, W. N., Cremer, J. E.:* The biochemistry of organotin compounds diethyltin dichloride and triethyltin sulphate, Biochem. J., 61 (1955) 406–418.
28. *Aldridge, W. N.:* The inhibition of erythrocyte cholinesterase by tri-esters of phosphoric acid. 3. The nature of the inhibitory process, Biochem. J., 54 (1953) 442–448.
29. *Davies, D. R., Green, A. L.:* The chemotherapy of poisoning by organophosphate anticholinesterases, Brit. J. indust., Med., 16 (1959) 128–134.
30. *Frawley, J. P., Hagan, E. C., Fitzhugh, O. G.:* A comparative pharmacological and toxicological study of organic phosphateanticholinesterase compounds, J. Pharmacol, 105 (1952) 156–165.
31. *Davison, A. N.:* The mechanism of the inhibition of decarboxylases by isonicotinyl hydrazide, Biochim. Biophys. Acta, 19 (1956) 131–140.
32. *Davison, A. N.:* The mechanism of the irreversible inhibition of rat-liver monoamine oxidase by iproniazid (Marsilid), Biochem. J., 67 (1957) 316–322.
33. *Aldridge, W. N., Barnes, J. M., Denz, F. A.:* Biochemical changes in acute beryllium poisoning. Brit. J. exp. Path., 31 (1950) 473–484.
34. *Aldridge, W. N., Liddell, H. F.:* A new method for the microdetermination of beryllium with particular reference to its determination in biological materials, Analyst, 73 (1948) 607–613.
35. *Denz, F. A.:* The histochemical detection of beryllium, Quart. J. micro. Sci., 90 (1949) 317–321.
36. *Cheng, K. K.:* Experimental studies on the mechanism of the zonal distribution of beryllium liver necrosis, J. Path Bact., 71 (1956) 265–276.

37. *Aldridge, W. N.:* Beryllium and alkaline phosphatase, Nature (Lond), 165 (1950) 772.

38. *Magee, P. N., Stoner, H. B., Barnes, J. M.:* The experimental production of oedema in the central nervous system of the rat by triethyltin compounds, J. Path. Bact., 73 (1957) 107–124.

39. *Aldridge, W. N., Cremer, J. E.:* Organo-tin-dithizone complexes. The colorimetric determination of diethyltin and triethyltin compounds, Analyst, 82 (1957) 37–43.

40. *Cremer, J. E.:* The metabolism in vitro of tissue slices from rats given triethyltin compounds, Biochem. J., 67 (1957) 87–96.

41. *Stoner, H. B., Threlfall, C. J.:* The biochemistry of organotin compounds. Effect of triethyltin sulphate on tissue phosphates in the rat, Biochem. J., 69 (1958) 376–385.

42. *Aldridge, W. N.:* The biochemistry of organotin compounds. Trialkyltins and oxidative phosphorylation, Biochem. J., 69 (1958) 367–376.

43. *DuBois, K. P., Doull, J., Coon, J. M.:* Studies on the toxicity and pharmacological action of octamethyl pyrophosphoramide (OMPA; Pestox III), J. Pharmacol., 99 (1950) 376–393.

44. *Blaschko, H., Hagen, J. M., Hagen, P.:* Mitochondrial enzymes and chromaffin granules, J. Physiol, 139 (1957) 316–322.

45. *Whittaker, V. P.:* The nature of bound acetylcholine, Biochem. J., 68 (1958) 21P.

46. *Peters, R. A.:* Biochemistry of some toxis agents. I. Present state of knowledge of biochemical lesions induced by trivalent arsenical poisoning, Bul.. J. Hopkins. Hosp., 97 (1955) 1–20.

47. *Krebs, H. A.:* Excursion into the borderland of biochemistry and philosophy. I. Teleological considerations in biology, Bull. J. Hopkins Hosp., 95 (1954) 45–51.

48. *Aldridge, W. N., Lovatt-Evans, C.:* The physiological effects and fate of cyanogen chloride, Quart. J. exp. Physiol. 33 (1946) 241.

49. *Aldridge, W. N.:* The estimation of micro quantities of cyanide and thiocyanate, Analyst, 70 (1945) 474–475.

50. *Aldridge, W. N.:* The conversion of cyanogen chloride to cyanide in the presence of blood proteins and sulphydryl compounds, Biochem. J., 48 (1951) 271–276.

51. *Cooper, J. R., Brodie, B. B.:* The enzymatic metabolism of hexobarbital (EVIPAL)., J. Pharmacol, 114 (1955) 409–417.

52. *La Du, B. N., Gaudette, L., Trousof, N. Brodie, B. B.:* Enzymatic dealkylation of aminopyrine (pyramidon) and other alkylamines, J. biol. Chem., 214 (1955) 741–752.

53. *Axelrod, J.:* The enzymatic demethylation of ephedrine, J. Pharmacol., 114 (1955) 430–438.

54. *Axelrod, J.:* The enzymic cleavage of aromatic ethers, Biochem. J., 63 (1956) 634–639.

55. *Mitoma, C., Udenfriend, S.:* Enzymatic hydroxylation of aromatic drugs, J. Pharmacol., 113 (1955) 40.

56. *Davison, A. N.:* The conversion of schradan (OMPA) and parathion into inhibitors of cholinesterase by mammalian liver, Biochem. J., 61 (1955) 203–20.9

57. *Fenwick M. L., Barron, J. R., Watson, W. A.:* The conversion of dimefox into an anticholinesterase by rat liver in vitro, Biochem. J., 65 (1957) 58–67.

58. *Murphy, S. D., DuBois, K. P.:* The influence of various factors on the enzymatic conversion of organic thiophosphates to anticholinesterase agents. J. Pharmacol., 124 (1958) 194–202.

59. *Magge, P. N., Vandekar, M.:* Toxic liver injury. The metabolism of dimenthylnitrosamine in vitro, Biochem. J., 70 (1958) 600–605.

60. *Cremer, J. E.:* The biochemistry of organotin compounds. The conversion of tetraethyltin in triethyltin in mammals, Biochem. J., 68 (1958) 685–692.

61. *Cremer, J. E.:* Biochemical studies on the toxicity of tetraethyllead and other organo-lead compounds, Brit. J. indust. Med. (1959).

62. *Murphy, S. D., DuBois, K. P.:* Quantitative measurement of inhibition of the enzymatic detoxification of malathion by EPN (ethyl p-nitrophenyl thionobenzenephosphonate), Proc. Soc. exp. Biol. Med., 96 (1957) 813–818.

63. *Murphy, S. D., Anderson, R. L., DuBois, K. P.:* Potentiation of toxicity of malathion by triorthotolyl phosphate, Proc. Soc. exp. Biol. Med., 100 (1959) 483–487.

64. *Aldridge, W. N.:* Tricresyl phosphates and cholinesterases, Biochem. J., 56 (1954) 185–189.

65. *Bernard, C.:* La science expérimentale, Baillière, Paris, (1875) p. 237.

Sadržaj

TOKSIČNOST I ENZIMI

Toksičnost supstancija često se može protumačiti njihovim djelovanjem na enzime. Sve veće poznavanje reakcije i svojstava enzima, kao i poznavanje distribucije enzima u tkivima organizma pokazalo je mnoge načine, na koje mogu toksične supstancije djelovati. Neke od tih mogućnosti raspravljane su u ovom članku.

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