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&
WEST
editors

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Preface

This volume contains six reviews, some of which have a chemical bias while others concentrate on biological topics. The first chapter describes the advantages of computerized literature searching in the medicinal sciences and, in a sample output which covers a few months' literature, illustrates how valuable the MEDLARS system can be. Then follows a chapter on the medicinally and toxicologically important coumarins.

Enzymes, so often popular for explaining the mechanism of drug action and detoxification, form the subject matter of chapter 3. The present state of knowledge of the relationship of chemical structure of polycyclic hydrocarbons to the likelihood of carcinogenicity is reviewed in chapter 4. The recently developed application of free energy calculations to the action of chemicals on biological systems often leaves the average medicinal chemist bewildered, and chapter 5 aims to introduce and explain the physical chemical concepts involved so that the reader who is interested may be better equipped to read the specialised reviews which are available. In the last chapter, a very active facet of synthetic medicinal chemistry – the synthesis of nitriles – is reviewed.

We would like to thank our authors who have been so patient during the transfer of responsibility to our new publishers, and also the owners of copyright of diagrams which are reproduced. We are also grateful to the publishers for their co-operation and assistance. It is hoped that in future a casebound volume of this Series will be published annually.

April 1973

G.P. Ellis
G.B. West

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1 MEDLARS Computer Information Retrieval

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National Lending Library for Science and Technology, Boston Spa, Wetherby, Yorkshire, LS23 7BQ

INTRODUCTION

All scientists will agree that scientific progress depends on communication. Without the transmission of results and theories from one to another, each member of the community starts at square one. Direct person-to-person informal communication may be immediately rewarding and highly effective once the channel is established; formal communication, through the learned periodicals is more rigid, but much less dependent on chance.

However practically important it may be, the search for information in the literature is seldom as interesting as personal communication or as exciting as discovery. Yet everyone is aware of the penalty of not knowing about relevant published data. A cautious welcome should be given to any new service which offers to reduce the tedium and the uncertainty of searching the literature. Computer retrieval does this, but like any powerful machine, it must be understood and skilfully used.

COMPUTER INFORMATION RETRIEVAL

Searching a computer data base consists of imagining what words will have been assigned to relevant papers and instructing the computer to find such papers and print out a list of the references. The simplest kind of system depends on the titles given by authors, and much imagination may be necessary as various synonyms may have been used. The least trouble arises from a fairly simple chemical such as 2-chloroethanol. A drug such as cannabis, however, has a wider range of synonyms, and for a general concept such as 'behaviour', an enormous range of words may have been used.

In a system such as MEDLARS, the vocabulary is controlled and limited, and the indexer assigns CANNABIS whether the author uses 'cannabis', 'marihuana' or 'pot'. Individual chemical substances rarely appearing in the medical literature are omitted, the problem being overcome by assigning both ALCOHOL, ETHYL and CHLORINE for the chemical 2-chloroethanol. There is a small risk of false retrieval and in practice it is far outweighed by the advantages of the controlled vocabulary.

MEDLARS

MEDLARS stands for *Medical Literature Analysis and Retrieval System.* It was set up by the US National Library of Medicine (NLM) and became fully operational in January 1964. The indexing and searching operations have now been decentralised (see below for a list of National MEDLARS Centres), but central processing is still controlled by NLM.

Altogether about 200 000 articles a year, taken from 2300 medical and biological journals, are included in the system, just over a half of these being in English. This broad coverage gives the system its first great advantage, as no individual searcher can hope to scan more than the few 'core' journals in his subject. Even when these carry most of the important articles, this approach must be distinguished from the MEDLARS coverage which should be almost complete.

Each article has assigned to it about ten subject headings describing its contents. Three or four of these, 'IM' or 'Print' headings, reflect the main theme of the article. The remainder reflect minor themes, and such concepts as HUMAN, ANIMAL EXPERIMENTS, CHILD, or the names of experimental animals or techniques.

The record which is entered into the MEDLARS computer system at NLM, consists of the author's names, title, bibliographic reference, and these subject

headings. Each month the computer produces two separate kinds of output. One is a magnetic tape used to drive a high-speed photocomposing machine which sets the type for *Index Medicus.* This is printed and distributed to about 300 libraries in the United Kingdom and to libraries in many other countries. In *Index Medicus* the title of each article is listed under the three or four 'print' headings to which it was assigned.

The other monthly product is a magnetic tape containing the full record for each article, including all the subject headings. This is duplicated and a copy is sent to each MEDLARS search centre. A variety of other products such as regular bibliographies of particular subject areas is also obtainable.

All of the MEDLARS centres conduct their searches on the same principles, although there are considerable superficial differences due to the variety of different computers used. The UK MEDLARS service has been in operation since May 1966, using the ICL KDF9, originally at Newcastle University but later on the Nottingham University machine. A completely new set of programs has now been written for the ICL 4/50 to take advantage of disc storage, and to allow for vocabulary expansion which is expected in MEDLARS 2. The machine actually used belongs to the UK Chemical Information Service at Nottingham.

SEARCH FORMULATION

Papers are required, say, about the effect of hallucinogenic drugs on behavioural patterns in mice. Any such paper should contain (a) the name of such a drug *and* (b) some words descriptive of behaviour patterns *and* (c) the word 'mice' (or 'mouse'). There are half a dozen MEDLARS subject headings for hallucinogenic drugs: such as HALLUCINOGENS, CANNABIS, and LYSERGIC ACID DIETHYLAMIDE, but more than 50 behavioural terms which might be appropriate, e.g. BEHAVIOUR, ANIMAL; NESTING BEHAVIOUR; LEARNING, and naturally MICE must be included.

A relevant paper might be listed in the published *Index Medicus* under any one or more of the drug or behaviour terms. This makes the 'hand search' (non-computer) a tedious proposition. The computer can be given three lists of terms and instructed to select any paper which has at least one term for each list. Thus the computer gives a bibliography of all those papers about hallucinogens *and* behaviour *and* mice. The hand search involves looking at all the titles under all the hallucinogens to see if they refer to behaviour and mice, all the papers under all the behaviour terms, and so on. Very often, of course, the title alone does not make clear whether the paper is relevant. (For example, a paper entitled 'Les incapacitants psychiques: moyens d'étude expérimentale' appears under HALLUCINOGENS).

Roughly speaking, the computer-produced bibliography is more compact by an order of magnitude for every *'and'* in the search strategy; in one study it was found that a third of the relevant papers retrieved in a hundred searches could not have reasonably been found in a 'hand' search because of incompletely informative titles.

COMPUTER PROCESSING

In the early search programs used at NLM and on the KDF9 computer in the United Kingdom, the data base was contained on many reels of magnetic tape. In making a search, it was necessary to scan through all the tapes looking for references to which the appropriate subject headings had been applied. This occupied many hours of computer time. Fortunately, many different questions were checked simultaneously, thus sharing the cost. Unfortunately, questions therefore had to be gathered into weekly or fortnightly batches, slowing the turn-round time.

The new programs make use of 'inverted file' storage on magnetic discs. The initial cost of setting up such files is quite high, but searches can be made quickly and more cheaply.

For the normal MEDLARS service, the scientist in need of information discusses his problem with a trained librarian-information officer. Between them, they draw up a list of the subject headings and develop logical statements which define what combinations of these terms are relevant.

In batch processes, these search formulations are keypunched on to cards and read into the computer. An editing process checks the validity of the terms against a dictionary; the search process then retrieves a list of relevant references from the inverted file; and finally a print program retrieves these references and prints them out in intelligible form.

The inverted search process, in conjunction with modern developments in computing, lends itself to on-line information retrieval. The librarian-information officer, or even the scientist himself, sits at a typewriter terminal connected, over telephone lines, to the computer. He explores the dictionary, establishes the search formulation, and then the computer searches for the references and prints them out before his eyes. In the USA this service is known as MEDLINE and is the main means of access to the MEDLARS data base. Various experimental services of this kind are in operation at European MEDLARS centres, but the relatively higher cost of telephone communication here makes it more expensive than batch searching.

In addition to retrospective searches of the data base, most MEDLARS cen-

tres offer a current awareness service. The references on each month's new tape are searched for the new items on any subjects desired. They may be highly specialised searches tailor-made for an individual or a small research group or more general ones. The latter can be produced in the form of multiple copies, thus sharing the computer cost. For example, the UK MEDLARS service produces a monthly bibliography on cards on the subject of mental retardation and about twenty copies are distributed. The cost is about a third of that of an individual current awareness search.

COMMUNICATING A MEDLARS SEARCH REQUEST

The computer is a powerful but literal-minded servant and naive attempts at retrieving references may lead to being swamped, like the sorcerer's apprentice. On the other hand, unfamiliarity with some habitual indexing rule may cause relevant papers to be missed. Trained search editors, thoroughly familiar with the indexing rules, are therefore used to prepare the formulations. However, the final arbiter as to what is relevant, is the scientist-user. The channel of communication between him and the search editor makes or breaks the service. To this end, appreciation courses are organised and staff from almost every medical and pharmaceutical library in the UK have attended them. There is also an explanatory handbook available on request.

A brief introduction such as this cannot do more than indicate the general nature and scope of MEDLARS. Readers who wish to explore further the possibility of using it are advised to consult their medical library (if in the UK) or their nearest national MEDLARS centre.

SAMPLE BIBLIOGRAPHY

As an example of MEDLARS, a sample bibliography on the topic of 'Chemotherapy of allergy' is appended. It is a rather simple, general search. Any paper was retrieved which had *either* one or more of:

HYPERSENSITIVITY, DELAYED
DERMATITIS, CONTACT
POISON IVY DERMATITIS
HYPERSENSITIVITY, IMMEDIATE
ANAPHYLAXIS
ANGIONEUROTIC EDEMA
ARTHUS PHENOMENON
ASTHMA
DERMATITIS, ATOPIC
HAY FEVER
RESPIRATORY HYPERSENSITIVITY
SERUM SICKNESS
URTICARIA

and the qualifying subheading
DRUG THERAPY

The references in this sample come from the October to December 1971 tapes. Copies of a more up-to-date sample are available at the price of £1.00 from the UK MEDLARS Service.

MEDLARS SAMPLE SEARCH – THE CHEMOTHERAPY OF ALLERGY

Cromolyn Sodium (Intal), A New Antiasthmatic Drug.
Eng

Med Lett Drugs Ther 13 63–4 23 Jul 71
AEROSOLS::ASTHMA/DRUG THY::CHROMONES/THER USE::CLINICAL RESEARCH::DISODIUM CHROMOGLYCATE/ADV EFF::HUMAN::PLACEBOS

Ankier SI
Disodium Cromoglycate and Inhibition of Passive Cutaneous Anaphylaxis.
Eng

Int Arch Allergy Appl Immunol 41 161–62 1971
ASTHMA/IMMUNOL::CHROMONES/THER USE::CLINICAL RESEARCH::DISODIUM CROMOGLYCATE/THER USE::HUMAN::PASSIVE CUTANEOUS ANAPHY::PLACEBOS

Cade JF Pain MC
Role of Bronchial Reactivity in Aetiology of Asthma.
Eng

Lancet 2 186–8 24 Jul 71
ACUTE DISEASE::ADOLESCENCE::ADRENAL CORTEX HORMONES/THER USE::ADULT::AEROSOLS::AGE FACTORS::ASTHMA/DRUG THY::BRONCHI/DRUG EFF::DISODIUM CROMOGLYCATE/THER USE::FEMALE::HUMAN::INHALATION THERAPY::ISOPROTERENOL/PHARMACO::MALE::MENSTRUATION::METHACHOLINE COMPOUNDS/PHARMACO::MIDDLE AGE::SEX FACTORS::SPIROMETRY::STEROIDS/THER USE::TIME FACTORS

Farrow LJ Holborow EJ Brighton WD
Reaction of Human Smooth Muscle Antibody with Liver Cells.
Eng

Nature (New Biol) 232 186–7 11 Aug 71
ALKANES/PHARMACO::ANIMAL EXPERIMENTS::ANTIGENANTIBODY REACTIO::AUTOANTIBODIES/ANALYSIS::CHICK EMBRYO::FLUORESCENT ANTIBODY TEC::GAMMA GLOBULIN 19S/ANALYSIS::HEPATITIS/IMMUNOL::HUMAN::IGG/ANALYSIS::IMMUNE SERUMS::LIVER/IMMUNOL::LUNG/IMMUNOL::MUSCLE SMOOTH/IMMUNOL::RATS:TISSUE CULTURE

Glazer I Racz I Molho M
Double Blind Single Crossover Clinical Evaluation of Disodium Cromoglycate in Bronchial Asthma.
Eng

Int Arch Allergy Appl Immunol 41 161–2 1971
ASTHMA/DRUG THY::CHROMONES/THER USE::DISODIUM CROMOGLYCATE/THER USE::HUMAN::INHALATION THERAPY::ISOPROTERENOL/THER USE::RESPIRATORY FUNCTION TES::SKIN TESTS

Grothaus EA Flye MW Unis E Amos DB
Human Lymphocyte Antigen Reactivity Modified by Neuraminidase.
Eng

Science 173 542–4 6 Aug 1971
ANTIGENANTIBODY REACTIO/DRUG EFF::CYTOTOXICITY TESTS/IMMUNOL::HUMAN::LYMPHOCYTES/IMMUNOL::NEURAMINIDASE/PHARMACO::TISSUE CULTURE

Guibert L Wolfromm R Bernard JG Vallery-Radot C
(Value of Combined Aluminum Hydroxide and Allergenic Extracts in Desensitizing Treatments. 1. The Phenomenon of the Skin Reaction at a Distance from the Allergen Injection Site, Induced by Aluminum Hydroxide).
Fr

Intéret de l'Association Hydroxyde d'Aluminium-Extraits Allergéniques dans les Traitements de Désensibilisation. 1. Phénomène de la Réaction Cutanée à Distance du Point d'Injection de l'Allergène, Provoque par l'Hydroxyde d'Aluminium.

Rev Fr Allergol 11 123–8 Apr–Jun 71
ALLERGENS/THER USE::ANTACIDS/THER USE::ANTIBODY FORMATION/DRUG EFF::ANTIGENANTIBODY REACTIO/DRUG EFF::DESENSITIZATION::ENGLISH ABSTRACT::HUMAN::HYPERSENSITIVITY/THERAPY::IMMUNIZATION::INJECTIONS INTRADERMAL::SKIN TESTS

Haruna H
Studies of Histamine, Serotonin and these Pexic Actions in Asthmatic Children.
Eng

Paediatr Univ Tokyo 18 32–5 Dec 70
ANIMAL EXPERIMENTS::ASTHMA/DRUG THY::CHILD::CHROMONES/THER USE::DISODIUM CROMOGLYCATE/THER USE::GAMMA GLOBULIN/THER USE::GUINEA PIGS::HISTAMINE/PHYSIOLY:HUMAN::RATS::SEROTONIN/PHYSIOLY::

Henson EC Collins DA Izard SR Brunson JG
Inhibition of the Tuberculin Reaction in Guinea Pigs.
Eng

Int Arch Allergy Appl Immunol 40 729–38 1971
ANIMAL EXPERIMENTS::ANTIGENANTIBODY REACTIO/DRUG EFF:CELL MEMBRANE/DRUG EFF:DRUG SYNERGISM::EPINEPHRINE/ADMIN+D:: GUINEA PIGS::HYPERSENSITIVITY DELAYE/PREV+CON::IMMUNIZATION:: IMMUNIZATION SECONDARY::INJECTIONS INTRAPERITON::INJECTIONS, SUBCUTANEOUS:PHENOTHIAZINES/ADMIN+D::TUBERCULIN TEST

Horsch A Rapp W
(Effect of Oxyphenbutazone on Immunologic Reactions. 2. Passive Cutaneous Anaphylaxis (PCA) Treated with Oxyphenbutazone, Cortisone and Cyclophosphamide).
Ger
Die Beeinflussung Immunologischer Reaktionen durch Oxyphenbutazon. 2. Die Passive Cutane Anaphylaxie (PCA) unter der Behandlung Mit Oxyphenbutazon, Cortison und Cyclophosphammid.

Arzneim Forsch 21 769–72 Jun 71
ANIMAL EXPERIMENTS::ANTIGENANTIBODY REACTIO/DRUG EFF: CORTISONE/PHARMACO::CYCLOPHOSPHAMIDE/PHARMACO::ENGLISH ABSTRACT::ERYTHEMA::FEMALE::GUINEA PIGS::IMMUNE SERUMS/ ADMIN+D::IMMUNOSUPPRESSION::IMMUNOSUPPRESSIVE AGENTS/ PHARMACO::INJECTIONS INTRADERMAL::MALE::OXYPHENBUTAZONE/ PHARMACO::PASSIVE CUTANEOUS ANAPHY/DRUG EFF::RABBITS::SERUM ALBUMIN/ADMIN+D

Ionescu-Goga S Scherf HR
(Methodical Testing of Immunosuppressive Agents)
Ger
Methodische Untersuchungen zur Prufung von Immunsuppressiva.

Arzneim Forsch 21 952–4 Jul 71
ANIMAL EXPERIMENTS::ANTIBODY FORMATION/DRUG EFF: CYCLOPHOSPHAMIDE/THER USE::ENGLISH ABSTRACT::HYPERSENSITIVITY:: HYPERSENSITIVITY DELAYE/DRUG THY::IMMUNIZATION:: IMMUNOSUPPRESSION::IMMUNOSUPPRESSIVE AGENTS/THER USE::MALE:: RATS::SKIN TESTS::TOXINS/PHARMACO

Sinka L Danilla T
(Experiences with Locasalen Ciba Ointment)
CZ
Nase Skusenosti S Mast'ou Locasalen Ciba.
Cesk Dermatol 46 71–8 Apr 71
ADULT::AGED::CHRONIC DISEASE::DERMATITIS ATOPIC/DRUG THY:: DERMATITIS CONTACT/DRUG THY::DRUG SYNERGISM::ECZEMA/DRUG THY::ENGLISH ABSTRACT::FEMALE::FLUMETHASONE/ADMIN+D:: FLOURINE/ADMIN+D::GLUCORCORTICOIDS/ADMIN+D::HUMAN::LUPUS ERYTHEMATOSUS DIS/DRUG THY::MALE::MIDDLE AGE::OINTMENTS:: PREGNANES/ADMIN+D::PSORIASIS/DRUG THY::SALICYLIC ACID/ ADMIN+D::

Stolting G Kienietz M
(Rectal Administration of Prednisone. Clinical Experience)
Ger
Zur Rektalen Anwendung von Prednison. Ein Erfahrungsbericht.
Med Welt 27 1146–7 10 Jul 71
ADOLESCENCE::BRONCHITIS/DRUG THY::CHILD::CHILD PRESCHOOL::
COLITIS ULCERATIVE/DRUG THY::DERMATITIS CONTACT/DRUG THY::
HUMAN::INFANT::INFANT NEWBORN::LARYNGITIS/DRUG THY::
NEURODERMATITIS/DRUG THY::PREDNISONE/ADMIN+D::SUPPOSITORIES::

Van Vunakis H Farrow JT Gjika HB Levine L
Specificity of the Antibody Receptor Site to D-Lysergamide: Model of a Physiological Receptor for Lysergic Acid Diethylamide.
Eng

Proc Natl Acad Sci USA 68 1483–7 Jul 71
AMINES::ANIMAL EXPERIMENTS::ANTIGENANTIBODY REACTIO/DRUG
EFF::BINDING SITES::CROSS REACTIONS::ERGOLINES::ERGONOVINE::
ERGOT ALKALOIDS::ERGOTAMINE::GUINEA PIGS::HAPTENS::HEMOCYANIN::
IMMUNE SERUMS::IODINE ISOTOPES::LYSERGIC ACID DIETHYLAMI::
LYSINE::MELATONIN::MESCALINE::PHENETHYLAMINES::POLYMERS::
PSILOCYBINE::RABBITS::RADIOIMMUNOASSAY::RECEPTORS DRUG::
SEROTONIN::SYMPATHOLYTICS::SYMPATHOMIMETICS::TRYPTAMINES/
PHARMACO/TYRAMINE::

LIST OF NATIONAL MEDLARS CENTRES

Australia
National Library of Australia
Canberra, A.C.T. 2600
Australia

Canada
MEDLARS Center
National Science Library
National Research Council of Canada
100 Sussex Drive
Ottawa 7
Canada

France
Centre de Documentation de l'INSERM
Centre Hospitalier de Bicêtre
78 ave du Général LeClerc
94 Kremlin-Bicêtre
Paris 16e
France

Germany
DIMDI
5 Köln 41
Postfach 520480
West Germany

Japan
The Japanese Information Centre
of Science and Technology
C.P.O. Box 1478
Tokyo
Japan

or

No. 5-2, 2 tyome, Nagatatyo
Tiyoda-Ku
Tokyo
Japan

Sweden
Biomedical Documentation Center
Karolinska Institutet,
Fack S-104
01 Stockholm 60
Sweden

Switzerland
World Health Organisation Library
Avenue Appia
1211 Geneva 27
Switzerland

USA
National Library of Medicine
8600 Rockville Pike
Bethesda
Maryland 20014

2 The Use of Enzymology in Pharmacological and Toxicological Investigations*

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INTRODUCTION

Today, the experimental techniques of enzymology are essential for the pursuit of inquiries in many biological disciplines, and investigators with only a meagre training in enzymology find it no easy task to extract the information relevant to their own interests from the enzymological literature [1–14]. This is especially true of investigators who are concerned with the biochemical effects of drugs, food additives, food contaminants, or environmental toxins. The ultimate effects

* See Editors' note added in proof on p. 84.

of any of these agents is a change in the biochemical performance of living cells, and enzymology is an essential tool for describing these. The present review is intended to provide a laboratory guide to enzymology for workers in biochemical pharmacology and related fields. It includes, in the final section, a list of just over 100 enzymes of special significance to pharmacological studies together with a minimum bibliography for each one. This represents less than 10% of the enzymes discovered up till the end of 1971.

Enzyme investigations have been undertaken in the past with several distinct and different objectives in mind. For this reason, enzymes are discussed in the text that follows in several distinct groups. The subsequent discussion is concentrated on those features of laboratory experimentation, which collectively provide good experimental designs for use in pharmacological and toxicological investigation.

A laboratory committed to this type of pharmacological research must of necessity utilise modern techniques borrowed from other branches of science. Among these are high speed centrifugation and an attendant knowledge of subcellular morphology at the electron microscope level. The technique of liquid scintillation counting is also essential for many studies. Review texts considered to be valuable are included in the bibliography [15–19]. It is assumed that the reader has some depth to his knowledge of physical instruments, and only one review (relating to fluorescence [20]) is included. Since enzyme determinations are dependent upon the measurement of initial reaction rate, a fair volume of mathematical computation is involved. Whenever possible this should be mechanised with the aid of either a programmed desk top calculator or a computer.

ENZYMES IN BLOOD

Only a few enzymes are specifically secreted by organs into the blood stream. These are the enzymes of blood coagulation, cholinesterase, and amylase [21]. Serum, in the main, is a passive receptacle for enzymes derived from the tissue cells and the formed elements of blood. Normally, the level of enzymes in serum is both low and constant. Since most of the enzymes present are derived from cells, it follows that these enzymes must be able to pass through the limiting membrane of the parent cell. This outward passage is accomplished either by diffusion through pores or alternatively by the aid of an active transport system. Except in those cases where enzyme secretion is a physiological process, active transport is unlikely. The loss of enzymes from cells is accelerated by tissue injury, and also by metabolic inhibitors like 2,4-dinitrophenol, iodoacetate, and carbon monoxide [22]. The implication that the retention by the cell of a