

Progress in Drug Research
Fortschritte der Arzneimittelforschung
Progrès des recherches pharmaceutiques
Vol.15

Progress in Drug Research
Fortschritte der Arzneimittelforschung
Progrès des recherches pharmaceutiques
Vol.15

Edited by · Herausgegeben von · Rédigé par
ERNST JUCKER, Basel

Authors · Autoren · Auteurs
S. SHARMA, S. COHEN, A. M. KAROW Jr.,
M. W. RILEY and R. P. AHLQUIST, J. W. MCFARLAND, H. UEHLEKE,
O. WINTERSTEINER, A. BURGER, E. R. GARRETT



1971

BIRKHÄUSER VERLAG BASEL
UND STUTTGART

Progress in Drug Research
Fortschritte der Arzneimittelforschung
Progress des recherches pharmaceutiques
Vol. 15

Edited by · Herausgegeben von · Rédigé par
Rudolf Jucker, Basel

Authors · Autoren · Auteurs
S. SHARMA, S. COHEN, A. M. KAROW JR.,
M. W. RILEY and R. P. AUGUST, J. W. McFARLAND, H. UHLMANN,
O. WINTERSTEINER, A. BURGESS, E. R. CARRETT



Birkhäuser Verlag Basel, 1971

ISBN 3-7643-0542-8

Printed in Switzerland

PROGRESS IN DRUG RESEARCH
FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG
PROGRÈS DES RECHERCHES PHARMACEUTIQUES
VOL. 15

PROGRESS IN DRUG RESEARCH
Fortschritte der Arzneimittelforschung
PROGRÈS DES RECHERCHES PHARMACEUTIQUES
VOL. 12

PREFACE

Twelve years have elapsed since the appearance of the first volume and it is with great pleasure that the Editor is now able to present volume 15. During these twelve years various fields of drug research have undergone important, partly revolutionary, changes. A number of these have already been dealt with, so that the series *PROGRESS IN DRUG RESEARCH* contains a comprehensive review of a substantial part of our current knowledge. The Editor is particularly grateful for the opportunity of transmitting to those connected with the development of drugs the extensive knowledge of the Authors, who, without exception, are themselves actively engaged in research.

Drug research is currently in a state of transformation: reconsideration in the light of the past and reorientation with a view to the future. To a large extent this is due to the tumultuous developments in the last 20 years, developments which are unparalleled in the history of medicine and the consequences of which cannot yet be completely evaluated. Unfortunately, however, the current situation is not devoid of its unpleasant and even tragic aspects, aspects which fall outside the research worker's sphere or influence. Those connected with drug research, be they in industry, in universities or in clinics, are aware of these problems, and, as a result of this awareness, are all the more in need of an aid which will assist them in ascertaining the current position and in fixing future goals. The Editor and the Authors hope that in this respect also *PROGRESS IN DRUG RESEARCH* will be useful to research workers and further the development of our science.

In addition to thanking the Authors and the Publishers, the Editor would like to express the hope that the international collaboration, which has hitherto succeeded to such an exceptional extent to the benefit of all, will continue so that the value of this series as a reference work will steadily increase. Judging from the manner in which the series has thus far been received and from the volumes currently in preparation, this hope appears to be justified.

This volume contains a collecting index of the volumes 12-15.

As suggested by various reviewers, we have included for the first time a subject index for volumes 1-15 and hope this will facilitate the encyclopaedic use of the series.

VORWORT

Seit dem Erscheinen des ersten Bandes sind zwölf Jahre vergangen, und der Herausgeber freut sich, der Fachwelt hiermit den 15. Band übergeben zu können. In dieser Zeitspanne haben auf verschiedenen Gebieten der Arzneimittelforschung wichtige, zum Teil umwälzende Entwicklungen stattgefunden; einzelne davon wurden in dieser Reihe bereits behandelt, mit dem Resultat, daß die FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG in ihrer Gesamtheit einen nicht unwesentlichen Teil unseres heutigen Wissens in zusammenfassender Darstellung enthalten. Der Herausgeber schätzt sich glücklich und ist dankbar für die Möglichkeit, mit diesem Werk das umfassende Wissen der Autoren, die ausnahmslos mitten in der aktiven Forschung stehen, zahlreichen in der Arzneimittelforschung Tätigen vermitteln zu dürfen.

Unser Forschungsgebiet befindet sich zurzeit in einer Phase des Umbruchs, der Besinnung auf Vergangenes und der Umoorientierung auf die Zukunft. Diese Situation ist zum Teil der äußere Ausdruck und das Resultat der stürmischen Entwicklung der letzten 20 Jahre, die in der Geschichte der Medizin ohne Parallele dasteht und deren Folgeerscheinungen noch gar nicht überblickt werden können. Zum Teil aber hängt die jetzige Lage mit unerfreulichen und auch tragischen Ereignissen zusammen, die außerhalb der Einflußsphäre der Arzneimittelforscher liegen. Die an der Arzneimittelforschung Beteiligten, seien sie Mitarbeiter der Industrie oder Forscher an Universitäten und Kliniken, sind sich der Problematik dieser Situation bewußt. Um so mehr bedürfen sie alle eines Hilfsmittels, das ihnen bei der Standortbestimmung und zur Neuorientierung dienen kann. Der Herausgeber und die Autoren hoffen, daß die FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG auch in dieser Hinsicht dem aktiven Forscher nützen und die Weiterentwicklung unserer Wissenschaft fördern können.

Zum Schluß dieser Betrachtungen möchte der Herausgeber nicht nur in gewohnter Weise den Autoren und dem Verlag danken, sondern darüber hinaus auch die Hoffnung aussprechen, daß die auf internationaler Ebene bisher so ersprießlich verlaufene Zusammenarbeit aller Beteiligten auch in Zukunft erhalten bleibt, um das Werk immer mehr zu einer wertvollen, viel benutzten Institution werden zu lassen. Die bisherige Aufnahme in Fachkreisen und die vorbereiteten weiteren Bände lassen diese Hoffnung als berechtigt erscheinen.

Dieser Band enthält einen Sammelindex der Bände 12-15.

Der Anregung einiger Rezensenten folgend, haben wir erstmals ein Sachverzeichnis der Bände 1-15 erstellt und hoffen, daß dies den Gebrauch der Serie noch erleichtern wird.

PRÉFACE

L'éditeur a aujourd'hui le plaisir de remettre au public le volume 15 de l'ouvrage, douze ans après la parution du premier. Durant ce laps de temps, les recherches pharmaceutiques ont subi, dans différents secteurs, des développements considérables, voire même, en partie, révolutionnaires; d'aucuns ont été déjà traités dans la présente série, si bien que les PROGRÈS DES RECHERCHES PHARMACEUTIQUES, pris dans leur ensemble, contiennent une part importante de nos connaissances actuelles sous forme d'aperçus généraux. L'éditeur est heureux de pouvoir, par ce canal, faire bénéficier les nombreuses personnes occupées aux recherches pharmaceutiques de la vaste science des auteurs, tous engagés activement dans la recherche et auxquels il se sent profondément obligé.

Notre champ de travail se trouve en ce moment dans une phase de transformation, de réflexion sur le passé et d'orientation nouvelle pour l'avenir. Cette situation est, en partie, la manifestation et le résultat du développement impétueux des vingt dernières années, développement sans précédent dans l'histoire de la médecine et dont les conséquences ne peuvent encore être évaluées; mais elle provient aussi, pour une part, d'événements malheureux, tragiques même, qui échappent à la sphère d'action de la recherche pharmaceutique. Ceux qui y collaborent, que ce soit dans l'industrie ou dans les universités et les cliniques, sont pleinement conscients des problèmes que pose cette situation nouvelle. Ils ont d'autant plus besoin d'un instrument qui puisse les aider à déterminer leur position et à se fixer une orientation nouvelle. L'éditeur et les auteurs espèrent que les PROGRÈS DES RECHERCHES PHARMACEUTIQUES s'avéreront utiles aux chercheurs, à cet égard aussi, et contribueront au développement ultérieur de leur discipline.

Au terme de ces considérations, l'éditeur ne voudrait pas seulement remercier, comme d'habitude, les auteurs et la maison d'édition, mais il tient en outre à exprimer l'espoir que la collaboration de tous les participants, qui s'est réalisée jusqu'ici au plan international d'une façon si satisfaisante, se poursuivra à l'avenir, pour que l'ouvrage devienne toujours davantage un instrument précieux et d'emploi fréquent. L'accueil qu'il a reçu dans les milieux intéressés et les articles à paraître dans les volumes suivants, en préparation, permettent de penser que cet espoir sera justifié.

Ce volume contient un index collectif des volumes 12-15.

Donnant suite au souhait de plusieurs auteurs de comptes rendus, nous avons incorporé, pour la première fois, une table des matières des volumes 1-15 et espérons que ceci facilitera l'usage de la série.

DR. E. JUCKER
SANDOZ AG, BASEL

原
书
缺
页

CONTENTS - INHALT - SOMMAIRE
VOL. 15

Ayurvedic Medicine - Past and Present	11
By S. SHARMA	
The Psychotomimetic Agents	68
By S. COHEN	
Pharmacology of Clinically Useful Beta-Adrenergic Blocking Drugs	103
By A. M. KAROW JR., M. W. RILEY and R. P. AHLQUIST	
On the Understanding of Drug Potency	123
By J. W. MCFARLAND	
Stoffwechsel von Arzneimitteln als Ursache von Wirkungen, Nebenwirkungen und Toxizität	147
Von H. UEHLEKE	
Basic Research in the US Pharmaceutical Industry	204
By O. WINTERSTEINER	
Cyclopropane Compounds of Biological Interest	227
By A. BURGER	
Drug Action and Assay by Microbial Kinetics	271
By E. R. GARRETT	
Index, Vol. 12-15	353
Subject Index - Sachverzeichnis - Table des matières, Vol. 1-15	381
Author and Paper Index - Autoren- und Artikelindex - Index des auteurs et des articles, Vol. 1-15	385

原 书 缺 页

Ayurvedic Medicine — Past and Present

By PANDIT SHIV SHARMA

1. <i>The Approach</i>	13
2. <i>Science and Religion</i>	13
3. <i>Introductory Summary</i>	15
3.1 Definitions	15
3.2 Sources of Valid Knowledge	17
3.3 The Three Basic Constitutions	17
4. <i>Historical Background</i>	20
4.1 Divergent Views: Haas and Johnston-Saint	21
4.2 Prof. Max Müller	22
4.3 Sir P. C. Ray	23
4.4 Other Indologists	24
4.5 Sanskrit	25
4.6 Ayurveda and Egyptian Medicine	27
4.7 Fantastic Mistakes	30
5. <i>Surgery in Ayurveda</i>	33
5.1 The Two Stimuli	33
5.2 Plastic Surgery	33
5.3 Iron Leg	34
5.4 Suppression of Knowledge	35
5.5 Dissection and Anatomy	36
5.6 Surgical Instruments	36
5.7 Accessories	37
5.8 Surgery in a Nutshell	38
5.9 Nursing	38
5.10 Hospitals	38
6. <i>A Few Case Histories</i>	39
6.1 Case 1. Asthma — Anaemia — Purulent Dermatitis — Haemolytic Jaundice — High Fever	39
6.2 Case 2. Infective Endocarditis	42
6.3 Case 3. Insomnia and Nervous Breakdown	45
6.4 Case 4. Pyelitis	47
7. <i>Ayurveda in Practice</i>	49
7.1 Laboured Interpretations	49
7.2 Modern Bed of Procrustes	50
7.3 Doshas	51
7.4 Vata	55
7.5 Vata in Health and Disease	56
7.6 The Vatic Diseases	57
7.7 Vata Exciting and Ameliorating Factors	58
7.8 Pitta in Health and Disease	59
7.9 The Paittic Diseases	60
7.10 Pitta Exciting and Ameliorating Factors	61
7.11 Kapha in Health and Disease	61
7.12 The Kaphaic Diseases	62
7.13 Kapha Exciting and Ameliorating Factors	63
8. <i>Some Explanatory Observations</i>	64
<i>Acknowledgments</i>	65
<i>References</i>	65

Ayurvedic Medicine — Past and Present

BY SHIV SHARMA

Editor's Note

On 10 December 1970, as the deadline for the publication of the present volume was drawing near, the Parliament of India, by a voice vote, *with not a single 'no' opposing the measure*, passed the Bill for the establishment of a statutory autonomous Central Council of Indian Medicine, which, in India, shall enjoy the same status as the Indian Medical Council. There are a number of modern doctors among the Members of the Parliament of India. This makes the passage of the Bill without opposition particularly significant. Earlier, about sixty amendments to various clauses of the Bill had been moved by several M.P.'s, *none of them opposing Ayurveda or the passage of the Bill*. The Parliament rejected them on the plea that an acceptance of even a single amendment, even if it favoured Ayurveda, would cause undue delay in the implementation of the Bill as, under the existing rules, the amendment would have to be referred back to the Rajya Sabha (Upper House) which had already approved of the Bill in the form in which it was presented before the Lok Sabha (Lower House). This is a striking proof of the survival value of Ayurveda, one of the oldest of the medical systems of the world, coming down to us from pre-historic times. In India, Ayurveda is taught in nearly a hundred Government or Government-recognized Ayurvedic Colleges. It already enjoys the existence of an autonomous Central Council of Research, a body equal in status to the ICMR (Indian Council of Medical Research). It is time that the rest of the medical world be introduced to Ayurveda in theory and practice. The writer is the Chairman of the Scientific Advisory Board of Ayurvedic Research, Government of India; Honorary Personal Ayurvedic Physician to the President of India, a Member of a number of Boards of Studies of Indian Universities having Faculties of Ayurveda and a popular Member of the Indian Parliament.

Editor

1. The Approach

"The Science of Life shall never attain finality. Therefore, humility and relentless industry should characterise your every endeavour and your approach to knowledge..."

The entire world consists of teachers for the wise and enemies for the fools. Therefore, knowledge conducive to health, longevity, fame and excellence, coming even from an unfamiliar source, should be received, assimilated and utilized with earnestness..." [1].

These words of wisdom were uttered by Punarvasu Atreya and recorded by his senior disciple, Agnivesha, 3,000 years ago. As sound advice on scientific attitude, they can hardly be improved upon, even today. At best, they can only be equalled. They embody the spirit which prevailed among the ancient Ayurvedic scientists for centuries.

Ayurveda, as you will find presently, is, both literally and factually, a very wide term, much wider than is actually required to denote a medical system, howsoever developed it may be. Since I am confining this note to the historical and medical aspects of Ayurveda, I have used the term '*Ayurvedic Medicine*' for the title of this note, to make it consistent with the content and the spirit of the treatise. However, in the Introductory Summary, I have permitted myself to include aspects other than historical and medical, to give a general idea of Ayurveda to the reader. This has been done with such brevity as to make the transgression on the coverage of the main subject practically negligible. I hope this arrangement will prove both informative and economical.

2. Science and Religion

Writing in an age when religion ruled supreme, with its firm hold on the minds of men, the Indian medical pioneers brought about a compromise and a working arrangement between religion and science which enabled the latter to prosper unhindered by religious dogmas and without arousing the slightest antagonism among the orthodoxy. This working arrangement between science and religion was disarmingly simple. If, in accordance with the prevalent laws of health and hygiene, a person was advised to rise in the small hours of the morning, long before sunrise, and asked to cleanse himself internally and externally, with detailed instructions on the care of the teeth, and on bathing and dressing, etc., he was also asked to say his prayers before starting his day's work. If the man was an atheist, he could cut out the observance of the prayer. He still obtained the benefit of the rest of the advice as much as the believer did.

It was a unique compromise between rigidity and flexibility – the rigidity of religion and the flexibility of science. The religion stood its ground. The science moved forward. And yet, the ancient Ayurvedists kept both in step with each other. Like the lotus leaf which remains submerged in water but

never partakes of its moisture and comes out always dry, the ancient Indian scientist accepted the religion as he did the manners and the etiquette of his times, and yet kept the science entirely free from the influence of religion on its growth and expansion.

Take the example of two identical surgical operations, appendectomies, in two different hospitals, by two different surgeons, one of them being a communist and the other a Roman Catholic, an ardent believer in God who would never start his day's work without saying his prayers. The latter, by sheer force of habit, would invoke the blessings of God to make his operation a success. The communist would have no truck whatsoever with the institution of prayer and perform his operation equally successfully. It would be observed that the scepticism of the non-believer and the faith of the believer are attitudes which do not, in any way, affect the actual technique of surgery in the least, in either case.

There are many modern surgeons and medical writers today who believe in religion. The only difference between the modern religious-minded surgeons and the surgeons of ancient India would lie in the former not introducing their practice of prayer in their text books of surgery whereas the ancients would record their entire routine in their works on science. In either case, the element of religion, whether confined to mere practice as at present, or extended to the records of science as in case of Ayurveda in ancient times, failed to make any dent in the scientific structure of the concept itself. This approach established a pleasant relationship between the scientist and the priest in ancient India. It created a setting in which a million Galileos could freely roam about without being molested or persecuted. Perhaps in no other country has the co-existence between science and religion been so cordial and indulgent as it has been in the case of Ayurveda in ancient India. This intelligent and mutually tolerant comradeship has continued to function to this day.

The great advantage science had over religion was its readiness to accept change. With religion, the static concept acquired what may be termed a conscience value. Therefore, it is very difficult for an ardent believer in religion to budge from a stand that his forbears had taken up in the remote past. Fortunately, there are no 'conscience values' attached to scientific beliefs. They can be cheerfully accepted, given up or modified to accommodate newer findings offering more cogent and consistent explanations for phenomena under observation or investigation. Ayurveda managed to promote this attitude amongst scientists without making any inroads into their religious beliefs and practices. In view of what has been said above, it will be advisable to confine this paper to the scientific concepts of Ayurveda exclusively, leaving out the references to religion including those to soul and to the Karma theory. Any reference to the supernatural or the metaphysical will be made only when found inevitable in presentation of the totality of the concept.

3. Introductory Summary

In introducing the Western reader to Ayurveda, I propose to make a departure from the common practice of giving the summary and the case histories at the end of the exposition of the subject. My reason for reversing the time-honoured arrangement is that, in the present case, the reader is more or less a stranger to the Ayurvedic concepts. If, at the very outset, he gets a bird's eye view of the entire exposition, he will have the advantage of getting the slant of the Ayurvedic outlook and a certain degree of familiarity with the general pattern of its theories in its approach to the problems of health and disease. That will bring up the reader to the level of the other readers of the papers on modern subjects where the summary is found at the end of the discussion. For, in the latter case, the readers are already familiar with the subject and the summary at the end merely serves as a short memorandum – a convenient aid to memory. In the present case, the purpose of the summary is in the nature of a brief introduction to the subject so that, while going through the main exposition, his mind remains familiar with the track along which it is progressing.

I also intend to give, later, a few case histories which will explain the reasons for the existence of Ayurveda during the 20th century.

3.1 Definitions

Ayurveda (Ayur = life; Veda = science), literally, means the 'science of life'. This covers the 'art of living'.

The *Prayojana* (main objective) of Ayurveda is *Dhatu-samya-kriya* (restoration and maintenance of the metabolic equilibrium) [2].

Swasthya (health) is defined as (a) *Dhatu-samya* (well balanced metabolism) plus (b) *Prasanna-atma-indriya-manah* (a happy state of the Being, the senses and the mind) [3]. 'Senses' here means the five organs of perception (smell, taste, sight, touch and hearing) coupled with the organs of action, namely, mouth, hands and feet, and organs of speech, excretion and reproduction.

Disease is defined as *Dukkha Samyoga*, i.e., 'contact with *Dukkha*' [4]. *Dukkha* has no exact equivalent in English language. It stands for physical discomfort, pain or suffering, as well as for mental anguish including the pangs of jealousy, fear, anger, avarice, hate, passion, etc., all that is unpleasant to the body and the mind.

Disease is fourfold: (1) *Agantuka* (adventitious), *Shariraka* (physical), *Manasika* (mental) and *Svabhavika* (natural) [5].

The *Agantuka* or the 'adventitious disease' results from external factors: cuts, bites, stings, injuries, accidents, etc.

The *Shariraka* or the 'physical disease' consists of internal ailments, nutritional and metabolic imbalances, growths and inflammations, diseases of infection and tissue degeneration, etc. Infectious diseases, in Ayurveda, even though of external origin, are included in the physical disease, as no infection takes place in the presence of immunity – an internal trait.

The *Manasika* or the 'mental disease', in Ayurveda, differs from the 'mental disorders' of the modern medicine. Diseases like insanity, schizophrenia, hypochondria, melancholia, paranoia, etc., which are partly mental and partly physical and which do respond to tranquilising drug treatment to a certain degree, do not represent the true Ayurvedic concept of the mental disease which is represented by states of anger and wrath, pride and vanity, greed and avarice, treachery, falsehood, indiscipline and uncurbed desires, hate, fear, cruelty, distress, sorrow, anxiety, unhappiness, laziness, etc.

The *Svabhavika* or the 'natural disease' covers birth, natural old age, death, natural hunger, natural thirst and natural sleep, as these phenomena do not fall outside the definition of disease, *Dukkha-Samyoga* (contact with unpleasantness) given above.

Generally speaking, the adventitious disease is treated surgically, the physical disease medically, the mental disease psychologically and the natural disease spiritually. This is Ayurveda in a nut-shell.

The inroads that the ideas of God, Soul, Karma and the cycle of birth and death have made into the Ayurvedic literature, do not affect the basic concept of metabolism in health and disease and the prophylactic and therapeutic approaches thereto. Their influence on the non-religious and main empirico-scientific aspects of Ayurveda is no more than that of a religious-minded surgeon's prayer for the success of a surgical operation which follows the prayer. The technique remains unaffected.

The definition of the Ayurvedic treatment boasts of the widest coverage of possible prophylactic and therapeutic approaches conceived by any system of medicine.

"A salubrious use of (a) drugs (*aushadha*), (b) diets (*anna*) and practices (*viuhara*), prescribed jointly and severally, (i) contrary to the cause of the disease, (ii) contrary to the disease itself, or (iii) contrary to both the cause and the disease, or (iv) similar to the cause of the disease, or (v) similar to the disease, or (vi), similar to both the cause and the disease, constitutes treatment (*upashaya*)" [6].

This accepts and covers all the principles of allopathy, homoeopathy and naturopathy, and explains why the Ayurvedic system is not in a position to disapprove of any of these 'pathies'. According to Ayurveda, they are alternate approaches to a common objective.

The definition of 'medicine' is even wider: "Nothing exists in the realm of thought or experience that cannot be used as a medicine (therapeutic agent)." It merely means that all existing phenomena, physical or physiological, psychic or emotional, e.g., anger and tranquility, joy and sorrow, fear and confidence, love and hate, foods and drinks, drugs (of mineral, vegetable or animal origin); fasts, massages, postures and exercises, desirable or undesirable experiences or situations; social, climatic or geographical conditions; laudatory or adverse comments, abuse and praise; good, bad or indifferent thoughts, etc., have a bearing on the body chemistry. There is nothing that can be experienced or conceived that does not influence the body or the mind of the individual to a