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THE INFLUENCE OF CLIMATE ON ALLERGY

EINFLUSS DES KLIMAS IN DER ALLERGIC IN DER PROVINZ
SEVILLA UND IHRE GRENZGEBIETE

Von

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I. Aufstellung der Allergielehre als Ausgang für unsere Studien.

Nach eigenen Beobachtungen und einer kurzen Durchsicht der bis jetzt erschienenen Mitteilungen, schliesse ich, dass der allergische Schock eine Bewegung der Schocksubstanzen darstellt, die ich wegen ihres Amincharakters, und ihrer wichtigen Rolle in den Korrelationen, „Biogene-Amine“ benenne, Guggenheim nachahmend. Die spezifische, an der Zellenwand beendete Reaktion ist die meiste Ursache, aber nicht die einzige dieser Aminbewegung, die, aus einer noch unbekannten Menge und Rhythmus besteht, aber stets verschieden seines Normalzustandes. Verschiedene äussere Zustände, hauptsächlich die sogenannten physischen Allergenen, veranlassen diese Bewegung, ohne dass vorher die spezifische Allergenen-Reagin Reaktion zustande kommt, was für uns die Bedeutung hat, einen allergischen Schock ohne spezifischen Antikörper hervorzurufen. Demnach stützt sich nicht die allergische Persönlichkeit auf eine spezifische Sensibilität wegen vorhandener spezifischer Antikörper, sondern an die Fähigkeit dieser

Aminbewegung, auch wenn keine spezifischen Antikörper vorhanden sind; deshalb glaube ich, obwohl die meteorologischen Faktoren, die sich von Zeit zu Zeit verändern und so das Klima hervorrufen, einen Allergiker beeinflussen können, sodass die Aminbewegung erzeugt wird, die einen allergischen Schock auslöst.

II. Arbeitsmethode.

Die experimentelle Methode ist nicht verfolgt worden, sondern die direkte Patientenbeobachtung nach stadistischer Methode, und damit Grundbeweise gestellt worden, dass diese mit bester Garantie studiert sind. Der Korrelationsindex der meteorologischen Veränderungen des Klimas und die Beschwerdenintensität von 1,300 Asthmatikern, die elf Jahre beobachtet wurden, ist berechnet und aufgestellt worden.

III. Korrelation zwischen meteorologischem Klima und Bronchialasthma.

Dieses Studium ist an Asthmatikern gemacht, die nur reine bakterielle Sensibilität und keine Exoallergen aufwiesen, um somit Irrtümer zu vermeiden. Wir gehen nun von zwei Gesichtspunkten aus: a) Möglichkeit die akuten Asthmaanfälle und plötzliche Verschlimmerung des chronischen Status zu fördern und b) Fähigkeit diesen chronischen Status aufrecht zu erhalten.

Eine sehr wichtige Rolle spielt in der Auslösung der akuten Anfälle, der niedrige und höhere atmosphärische Druck, welcher in der meteorologischen Sprache Zyklon und Antizyklon genannt wird, und ihre konsequenten Bildungen warmer und kalter Fronten, die Frontoklussion, und der Aufenthalt des Patienten in dem kalten oder warmen Zyklonkreis. Die akuten Anfälle haben mit dem gesamten Phänomen einen Korrelationsindex $+ 0,271 \pm 0,099$, ohne jedoch behaupten zu können, dass einige der Phänomen einen besonderen kräftigen Einfluss hätten, will man aber die ganz kleinen Unterschiede der Nummern schätzen, die Einflussserie ist folgendermassen: Antizyklon, Zyklon, warme Front Oklussion, warmer Zyklonkreis, kalte Front und als letztes kalter Zyklonkreis. Hingegen findet man gar keinen Einfluss in isolierten atmosphärischem Druck wegen seines niedrigen Korrelationsindexes, was beweist ist durch Beobachtung von zehn Patienten, bei denen während eines Fluges über Spanien kein Anfall ausgelöst wurde. Die niedrigen Temperaturen, hauptsächlich mit langer Dauer, helfen stark mit bei der Auslösung der Anfälle.

Die atmosphärische Feuchtigkeit beeinflusst nur dann, wenn die Trockenheit so hoch wäre, wie sie in Sevilla im Hochsommer zustandekommt. Die Windrichtung in unserem Gebiete hat keinen Einfluss, und der Föhn ist bei uns nicht beobachtet worden, trotzdem habe ich einmal die Gelegenheit gehabt ein föhnähnliches Phänomen zu registrieren, der eine regelrechte Katastrophe bei vier Patienten hervorriefte. Merkwürdig ist der Korrelationsindex — $0,362 \pm 0,095$ der akuten Anfälle und der Windgeschwindigkeit, trotzdem viel erregender Staub mitgeschleppt werden muss wie weiter berichtet wird. Die grossen elektrischen Phänome wie Blitze und Donner haben auch keinen Einfluss auf Anfälle, aber hingegen haben diese grosse Beziehung während der Anwesenheit von Wolkensystemen, hauptsächlich derer, die eine Front anmelden. Es wird aber stark betont damit, dass der Korrelationsindex eine imaginäre Zahl ist, wenn man einen Tag oder ein Jahr als Zeiteinheit berechnet; berechnet man aber eine Woche oder ein Vierteljahr als Zeiteinheit, erhält man wohl eine reale Zahl, aber garantelos; um eine völlige Garantie der Zahl zu erreichen, muss mit einem Monat als Zeiteinheit gearbeitet werden. Alle diese Tatsachen, und eigene besondere Beobachtungen führen mich zu dem Entschluss, dass die bis jetzt erörterten meteorologischen Veränderungen wirkliche biologische Angriffe auf den Organismus ausführen, und eine funktionelle Anpassung des Organismus verlangen. Der Angriff ist allerdings nie so stark, dass er die Dekompensation der biologischen Korrelation beim ersten Angriff auslöst; stets müssen es einige sein, um eine Dekompensation hervorzurufen, ein Monat dient mir dazu als Mittelwert. Nach diesem Misserfolg der Korrelationen erscheint die pathologische Antwort des Organismus ganz auf persönliche Art, wie z. B., der Asthmaanfall beim Asthmatiker. Das Wetter wirkt auf die Organismen etwas anders als die bekannten physischen Allergenen der Klinik.

Um den Wettereinfluss in der Verlängerung der chronischen Krisis zu beurteilen, habe ich die Bezeichnung „Tage-Krisis“ angenommen. Damit bezeichne ich die sämtlichen Tage die der Asthmatiker in dauernden Asthmaanfällen war, während einer bestimmten Zeitfrist. Unsere Statistik beruft sich stat der Zeiteinheit Monat, auf Zeiteinheit Vierteljahr. In diesen Zeitraum wirkt das Wetter anders als in die akuten Anfällen. Keinen Einfluss haben die Zyklonen, Antizyklonen, Fronten, der atmosphärische Druck und die Windrichtung und -kraft. Die niedrige Temperatur hat Einfluss, hauptsächlich wenn sie lange anhält; die höhere atmosphärische Feuchtigkeit verlängert die Krisis.

Betreffs des Aktionsmechanismus bin ich der Meinung, wenn die Zyklonen, Antizyklonen, Fronten und Okklusionen auf den Organismus wirken würden, durch die Veränderungen, die sie in der Temperatur, atmosphärischen Druck, Feuchtigkeit, usw. hervorrufen, dann wäre der Korrelationsindex zwischen diesen letzten meteorologischen Faktoren zu dem Wert der Asthmaanfalle zu dem Wert der Zyklonen oder Fronten untereinander in vollkommen Akkord. Der „ARAN“ von Curry ist meiner Meinung nach etwas undeutlich und unbestimmt, ausserdem ist seine Forschung in einer verschiedenen meteorologischen Zone gemacht, infolgedessen passen seine Ergebnisse nicht in unser Gebiet. Sehr interessant allerdings finde ich die Forschungen von Brandran, da er eine Korrelation zwischen Asthmaanfällen und plötzlichen Veränderungen des atmosphärischen elektrischen Potentials, elektronische Dispersionszeichen, magnetische Unruhe usw., gefunden hat. Jeder Zyklon wird mit einer elektrischen Veränderung begleitet, obgleich die elektrischen Veränderungen isoliert ausgelöst werden können. Janitzky hat bewiesen, dass eine 14–40 % der atmosphärischen Elektronladung in den Lungen zurückbleibt. Ich nehme an, dass die Wirkung des Klimas, in dem Ionenwechsel durch die Lungen mit der Atmosphäre zu suchen ist. Da diese Wetterwirkung sich nicht nur auf das Asthma, sondern auch auf Magenulkus, Angor pectoris, Hypertonie und acuten Bauchkoliken ausübt, bin ich zu dem Schluss gekommen, dass das Wetter nicht auf die Krankheit, sondern auf einen Organismus, der zufällig erkrankt ist, wirkt; leidet er an einer Krankheit in der die Korrelationen eine grosse Rolle spielen, dann erzeugt diese Wetterwirkung eine Dekompensation und dabei eine Verschlechterung des Zustandes. Dementsprechend wirkt nicht das Wetter auf die Krankheit, sondern auf den Mensch der erkrankt ist.

IV. Korrelation zwischen allergischem und meteorologischem Klima.

In diesem Abschnitt versuche ich zu entscheiden, ob das meteorologische Klima irgendwelche Einwirkung auf die Luftallergenen hat, so dass das Wetter ausser der direkten Wirkung auf die Patienten, noch eine indirekte Wirkung durch die Allergenen auslösen kann. Ein langdauerndes Studium von Staub, Pollen, Pilzen und Hefen, mit vielen Kurven und Tafeln werden davon vorgelegt. Die ganze Arbeit wird hier nur kurz zusammen gefasst.

Nur die Windgeschwindigkeit hat einen grossen einfluss auf den Staubwert. Es werden alle Korrelationsindexe zwischen Polen und meteorologischen Faktoren beschrieben, und ebenso ein ausführliches

Studium der Pilze gemacht. Die Pilze werden nicht nur nach Züchtungsmethode im Nährboden, sondern auch auf Objektträgern gezählt, die 24 Stunden dem Winde ausgesetzt waren, studiert. Ich finde diese letzte Methode als direkte Zählung der Pilze, die der Züchtungsmethode vorzuziehen. Erstens, auf den Objektträgern registriert man die Pilze, die im Nährboden nicht wachsen, zweitens, das Pilzbild passt besser zu der Krankensensibilität, und drittens, die Pilzwerte mit ihren entsprechenden atmosphärischen Veränderungen eignen sich auch besser.

Das Pilzbild unserer Umgebung besteht aus *Penicillium*, *Aspergillus*, *Alternaria*, *Mucor*, *Monillia*, *Botrytis*, *Fusarium*, *Cladosporium* und *Hormodendrum*, die ihrem häufigen Vorkommen nach reihenweise angeordnet sind. Stammende Statistiken aus verschiedenen Zonen der Iberischen Halbinsel werden untereinander verglichen, und komme ich zu dem Entschluss, dass ihre Unterschiede besser Zufalls- als Wirklichkeitsunterschiede sind. Die Hefekurve wird ebenfalls vorgelegt. Diese Hefen gehören zu den *Rhodotorulaceas*.

Der Wert der Pilze in der Atmosphäre hängt hauptsächlich von dem gesamten biologischen Zyklus jedes einzelnen Pilzes ab. Die meteorologischen spielen eine sehr kleine Rolle, nur die Windgeschwindigkeit wirkt deutlich auf sie. Etwas so ähnliches kommt bei den Pollen und Hefen vor.

Der biologische Zyklus der Pflanzen beeinflusst die Anwesenheit der Pollen in der Atmosphäre nur im Frühling. Ähnlich ist der Zyklus der Pilze. Das Maximum ist im Frühling und Minimum im Sommer. Der Mittelwert ist Herbst und Winter, aber manchmal im Herbst etwas höher als im Winter.

V. Korrelation zwischen allergischem Klima und Bronchialasthma.

Bis jetzt haben wir die Wirkung des Klimas auf die Asthmatiker und die Luftallergenen studiert, und jetzt müssen wir versuchen festzustellen, ob das Klima durch die Luftallergenen auf die Patienten auch wirkt; dazu brauchen wir nur die Korrelation zwischen den Luftallergenen und Asthmaleidenden zu kennen. Für dieses Studium teilen wir unsere Asthmatiker in drei Gruppen: Bakteriensensibilität, Pollenallergie und Pilzsensibilität.

Bakteriensensibilität. — Darunter stelle ich nur die Asthmatiker, die eine reine Bakteriensensibilität aufweisen, ohne dass andere Allergen eine Rolle spielen. Allerdings sind diese keine Luftbakterien, sondern es sind Mikroorganismen, oft Saprophyten, die in den Orga-

nismen, hauptsächlich in den Bronchien leben und sich entwickeln; diese Patienten sind ihre eigenen Allergenträger; da sie von aussen keine spezifischen Allergen empfangen, können sie nie ihre Verschlimmerungen den äusseren allergischen Einflüssen zuschreiben.

Pollenallergie. – Die Symptomintensität dieser Patienten, die nur im Frühling bei uns vorhanden sind, stimmt sehr genau mit der in der Atmosphäre vorhandenen Pollen überein; die Patienten beklagen sich, dass während der sonnigen und windigen Tage ihr Zustand sich verschlechtert; gleichzeitig registrieren wir während dieser auch den höchsten Pollenwert. Ich bin fest überzeugt, dass das Klima auf die Pollenleidenden nicht direkt sondern indirekt wirkt; ich will damit sagen, dass die Klimaveränderungen derartige Pollenveränderungen in der Luft hervorrufen, dass diese auf die Patienten wirken. Diese Wirkung ist so intensiv und so deutlich, dass kaum Platz bleibt, um an eine direkte Wirkung zudenken.

Pilzsensibilität. – Bei diesen Patienten, neben der Pilzsensibilität, ist ausserdem stets eine bakterielle vorhanden; Patienten mit anderer Sensibilität wurden ausgeschlossen. Selten sind die Patienten, die nur gegen einen einzigen Pilz sensibilisiert sind, meistens findet man Patienten die auf viele Pilze sensibilisiert sind. Die am häufigsten Vorkommenden sensibilisierenden Pilze sind *Ustilago* und *Tilletia*; gerade die, die im Nährboden nicht gezüchtet wurden, und konnten nur auf den Objektträgern beobachtet werden. Die Bedeutung der Pilze, nach ihrer Sensibilitätshäufigkeit beurteilt, stimmt nicht, trotz des häufigen Vorhandenseins in der Luft, mit jener überein. Es ist höchst wahrscheinlich, dass, solange wir die verschiedenen Pilzallergen noch nicht kennen, viele Fragen wie diese und andere ohne Antwort bleiben.

Der Wert „Tage-Krisis“ dieser Patienten haben einen Korrelationsindex $+0,458 \pm 0,18$ mit dem entsprechenden Monatspilzwert. Die Jahreszeit, in welcher der Zustand am schlechtesten ist, stimmt ziemlich genau mit der Periode, in welcher mehr Pilze in der Luft vorhanden sind, überein, Trotzdem, die täglichen Zustandsveränderungen stimmen nicht mit entsprechenden Veränderungen des Pilzwertes in der Luft überein.

VI. Geographische Verteilung unserer Asthmatiker.

Unsere Umgebung umfasst 120 Klm. im Umkreis, davon eine grosse Meeresküste, die Sand- und Lehm Böden hat, ein über 700 Meter hohes Gebirge, und der Rest gewöhnlicher Feldboden, aus der unsere Patienten zu uns kommen. Wir haben versucht zu entdecken, ob es

eine besondere geeignete Umgebung war, wo die Asthmatiker am häufigsten vorkamen, aber leider, die kleinen Unterschiede, die wir gefunden haben, müssen als Zufall angenommen werden.

VII. Schluss Synthese.

Der Einfluss des Klimas auf die Pollenpatienten ist nicht direkt, sondern indirekt; das Klima wirkt auf die Entwicklung, Wachstum und Reifung der Pflanzen; wenn der Frühling kommt und die Pflanzen reif sind, kann wirkt das Klima auf den Pollenwert der Luft. Wenn die Patienten sich über manche meteorologischen Faktoren beklagen, ist es deshalb, weil diese Faktoren eine Vermehrung der Pollen in der Luft hervorrufen.

Bei den bakteriensensibilisierten Patienten ist es etwas anders; wie schon erört, wirken hier keine äusseren Allergenen mit, und ist der ganze dritte Teil dieser Ponenz den bakteriensensibilisierten Patienten gewidmet, und infolgedessen, alles, was wir dort sagen, bezieht sich eben nur auf diese Patienten. Ich nehme also folgendes an: das Klima wirkt stark und stets direkt auf die bakteriensensibilisierten Patienten, und nie durch gleichzeitige Allergenveränderungen in der Luft.

Die Pilzpatienten müssen in einen Mittelpunkt gestellt werden; sie werden von dem Klima und von den Luftpilzen, jedes in getrenntem Sinne, ihren Einfluss erhalten; aber man darf nicht annehmen, dass erst das Klima über die Luftallergenen, und diese gleich auf die Patienten die Wirkung ausüben, wie bei Pollenallergie, sondern das Klima wirkt auf den Patienten, und die Allergenen auch auf den Patienten.

Zum Schluss müssen wir noch betonen, dass wir in dem Pilzbilde, beziehungsweise auf die Sensibilitätsbilder der Patienten, beide aus der Iberischen Halbinsel stammend, keine Unterschiede gefunden haben. Infolgedessen haben wir keine Ursache zu glauben, dass die schlechte oder gute Wirkung eines besonderen Klimas oder Umgebung nicht den Pilzbildern zuzuschreiben ist, sondern wir müssen stets an die meteorologischen Faktoren denken.

THE INFLUENCE OF CLIMATE ON ALLERGY

By

Professor M. DIAZ-RUBIO

It would be hard to summarize in a few words the problems actually set up by the influence of climate on allergy. We have evidently treated this theme in our paper presented to the Second Spanish Congress on Allergy, from which this present one can be considered as a summary. There the reader will be able to find clinical cases of interest on this subject as well as other data.

We could not reach any definite conclusions though some could be definite but because of the special characteristics of the field on which so little research has been done and so much must be done for a long time under varying circumstances and in different places, any conclusions serve more as a step for further work. What follows only concerns the climatic influences at Cadiz. Our experience has been based specially on clinical cases, although knowing the errors involved using this method, we have preferred it to all others because it allows a deeper and wider consideration of the problem, neither can we find any other method that is better. Our experiences is the same as that of *Rudder*.

The first difficulties lie in separating the climatic from the meteorological influences. The two influences must be considered separately. Atmospheric disturbances can be a source of error. It must be decided whether they characterise the regional climate or are only temporary accidents. Particularly so far as asthma is concerned we must consider the effect of climate on allergy. There are, however, so many factors that influence one another that for the analysis of a particular case the problem becomes very complicated, though we consider some points fundamental. There are few asthmatic or migrainous patients who do not notice the effect of a "change of locality" or a "change of weather".

Climate works upon the body in two different ways:—direct and indirect. Directly by increasing its reactivity or creating the paroxysm by itself, indirectly by modifying the allergic climate. These two different actions can act either in the same or opposite direction. Theoretically a definite climatic or atmospheric change may either increase the number of allergens in the air, thereby causing an allergic reaction, or it might lower the sensitivity. Different cases where both

possibilities were present have been seen. Moreover sometimes there is an additional factor to the main one.

On the other hand, we have not seen any interference between the precipitating factor and the allergic or physical factor other than an additional effect. When we saw our first cases which suggested such an idea we carefully looked for both factors in allergic diseases. We now think that the main climatic influence is on the allergic personality either enhancing or diminishing it. So we now know favourable and unfavourable climates common for all asthmatic patients. Yet although weather changes can act upon the allergic personality their principle role is a precipitating action.

Such an influence upon the reactive and vegetative personality does not surprise us, because excluding allergy, we know the existence of "atmospheric-sensitive" individuals. In such people atmospheric changes, especially cold and warm fronts and occlusions would cause a definite syndrome. All sorts of different types, whether composite or insensitive, have been considered and the existence or otherwise of these types has been discussed in our paper. We are convinced that there is such a condition as a meteoric sensitivity. The vegetative nervous system is repeatedly stimulated by the "vegetative change" expressed by any atmospheric change, though the response of the whole organism depends upon the state of the receivers.

Meteoric sensitivity at Cadiz is a very frequent phenomenon among healthy people. This is seldom related to the climatic characteristics of this region where there are frequent atmospheric changes. These circumstances facilitated the clinical study of this situation—commonly produced after the 'levante'—in atmospheric sensitive subjects. (The East wind is commonly called "levante" at Cadiz.) This clinical study is extensively referred to in our paper to the Allergy Congress. We insisted there upon the artificial division—children excepted—of the different types separated by *Curry*. In the combined type he includes all the meteoric sensitive individuals which is different from the scheme outlined by the author who has found a greater sensitivity in this type. Among children at Cadiz the sensitivity is normal until puberty when it disappears to reappear in the thirties without any relation to any illness. As *Curry* also pointed out meteorical sensitivity is shown in more or less all individuals including the hyporeactive cases where the clinical manifestation depends only on the intensity of the stimulus. Many frequently weather influences could cause a weather sensitivity. People living in quite a different climate from that of Cadiz during

their childhood without any clinical manifestation of a weather sensitivity may develop it after living for some time at Cadiz when an adult.

The weather sensitivity of healthy people and its clinical expression, specially when under weather changes, has many contact points with the migraine personality. Moreover migraine produced by a weather change parallels both situations, making them sometimes indistinguishable, as commonly the migraine or the asthmatic patient shows general symptoms of weather sensitivity. Finally, and unrelated to the allergenic climate there are a great number of asthmatics (or patients who are clinically like asthmatics) at Cadiz who have lived there for a long time. The static climate influence, at least in our region, will enhance the allergic personality especially during meteorological shocks.

We are sure that migraine and asthmatic patients have a "meteorotropic illness" character which is not necessarily related to the allergenic climate. So both will be influenced either by the climate itself or by the weather changes added to which the stationary "illness" character of the asthmatics is an added factor.

With the special atmospheric and geographical conditions at Cadiz the number of asthmatics seen there is naturally high with a similar distribution on the coast and inland. Interestingly the etiological per cent curve was similar to that described by *Jimenez Diaz* in Madrid. The number of bacterial asthmas which constitute most of the cases was practically equal. There are few house sensitive and pollen sensitive cases at Cadiz but we see more mould asthma cases (9.6 % against 6.6 % by *Jimenez Diaz*). Nearly half the cases at Cadiz show a mixed sensitivity to bacteria and moulds.

This is in keeping with the special local environmental allergic factors. Our published work agrees with *Orta* that the mould spore content of the air at Cadiz shows a high, though variable number, during different days and months. Our figures are higher than those given by *Canto* in Madrid, and similar to those given by *Cruz Auñon* and *Bolinches* at Seville. From May to August their number is so high compared with the average for the rest of the year that the difference could not be accounted for by any error. The greatest number of mould colonies are due to *Penicillium*, followed by *Cladosporium* and *Alternaria*, *Aspergillus*, *Macrosporium*, *Rhizopus*, *Monilla* and 22 less frequent genera. The first few genera are present all the year with some variation while the others are present for some months. In spite of all this and rather against what we would expect, the

figures for some months of the year are similar in Cadiz and Madrid.

The mould content of the air is influenced by weather changes. We have seen that when it is calm or with a sea breeze occurring with a warm front, the number of mould colonies found is high. This common occurrence coincides with the "levante" wind which blows over very wet land. The same wind will also under narrow limits increase the pollen content of the air of Cadiz.

The reason is an important factor with pollen asthmatics, who are always better in the Autumn and Winter, and in the city itself because of the low pollen count. With rare exceptions bacterial and mould asthmatics have a similar seasonal incidence. It should be noted that in some meteorological circumstances totally unexpected attacks occur without any allergic factor in the air. Sometimes in spite of large amounts of allergic material in the air there is no asthma. Such findings as frequent bacterial asthmatic attacks during the Summer show more clearly the formal influence of weather changes upon the attack. On these grounds if it is looked for it should be easy to find some relationship between the weather in asthmatic and migraine patients.

The cause either for the "meteorotropic illness" or for the asthmatic attacks must be considered against the whole background of the climate. Patients sometimes remark upon the influence of humidity upon their attacks, damp weather for some, dry for others, seem to alter the attacks. We have noticed looking for objective findings that sometimes the paroxysms occur with changes in humidity, especially when it is raised and this change is quickly produced. Yet no definite rules can be made as some of the attacks are not related to the degree of humidity.

Cold in most cases causes asthma and therefore should be common in Winter. Although there are no low temperatures during the Winter at Cadiz, Winter does not suit asthmatics there. But as has been pointed out for humidity, there are changes in temperature which frequently produce attacks, mainly if the temperature changes are associated with humidity changes and also if there is an increase or a decrease in atmospheric pressure especially if this is sudden or if there is a depression. The high humidity rate associated with a decrease in pressure and temperature predisposes to attacks. Yet many times we have seen that the same conditions caused no attack where previously similar atmospheric conditions always caused attacks.

Sudden changes in the wind are more important than the direction and spread, particularly if the wind is *Este*. Before this wind blows there are clinical manifestations in most of the atmospheric sensitive

asthmatic and migraine patients which are unrelated to any increase of allergic particles in the air. Low clouds precede—sometimes are co-incident—to the asthmatic attacks so the patients tell us and we have to study every attack in every case. Commonly the asthmatic attack occurs a few hours before the storm and ends with the storm.

Finally there are warm and cold fronts and occlusions which usually occur with the attacks. These explain the occasional attacks due to weather though it is impossible to make generalisations because the same situation can cause asthma in one patient and not in another, although both are in fact atmospheric sensitive and their meteorological sensitivity is similar. This second type of patient seldom has an attack in identical weather situations. The time just before the weather fronts seem to be most important. As has been stated previously the weather sensitive asthmatic and migraine patients cannot be classified as sensitive to a cold, warm or occluded front, because each can produce an attack.

As well as the importance of the intensity of a front or an occlusion causing an attack, there are other factors that are fundamental to understand the subject.

- (1) Atmospheric changes particularly when sudden are important. Repeated stimuli seem more effective than only one even if this one stimulus is much more intense. The second stimulus effects a patient "sensitized" by the first atmospheric change.
- (2) Reactivity is another very important factor. So that situations such as menstruation and fever are able to influence the onset of an asthmatic attack produced by a weather change.
- (3) Local climatic and weather accidents modify reactivity and so cause asthma which under different weather conditions but under similar allergic conditions would not occur. The reactivity of the patient is therefore closely related and widely influenced by the weather.

At present we are unable to detect which particular meteorological factor is responsible for these phenomena. Neither meteorological sensitivity, the physical hypothesis, or that based on electrical and magnetic field variations, or the new theory of the important role of Aran gas, can satisfactorily explain the facts. Probably not one but many factors would influence the vegetative nervous system. Additional factors, especially if they have opposite effects would produce repeated physical and chemical stimuli. It is suggested that these could act as the antigenic shock by liberating shock substances in a similar manner that weather factors can be eliminated by fever.

THE MECHANISM OF THE ACTION OF CLIMATE UPON ALLERGY

By

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Through recent investigations made by *Pedersen, Hellpach, De Rudder, Sardou, Van Der Elst, Curry, Laignel-Lavasttine*, etc. etc., meteorology has become an established science under the name of Bioclimatica or Meteoropathology when the study refers to troubles and diseases which might be caused in the human being by changes in the weather or the climate.

Meteorology to-day is an important chapter in medicine and in biogeography following upon a slow start caused by previous exaggerated reports. At the time of "meteorophilia" real amazement and surprise must have been caused by the attitude adopted by *Vallés*, hereafter physician to King Philip II, when on the occasion of an illness of this monarch, apparently serious and difficult to diagnose, a consultation was called of the most famous physicians of that epoch, when all passed through the royal bedchamber, doubting whether blood-letting should be practiced or not. All however agreed that it should not be carried out, seeing that the moon was not in the phase adequate for such a practice, to which *Vallés*, valiantly and with a certain scorn for his fellow physicians, replied gravely "Close the shutters of the bedchamber, I am going to give the medicine so quietly that not even the moon shall become aware of it."

Although now the science of the weather is being taken into consideration, there are still many points to be solved. We are still greatly ignorant about the mechanism of action of the weather on the body and also about what part the weather and variations in climate may play in the development of diseases or their aggravation.

Climate is still to be defined and the greater part of the definitions reviewed by Father *Romaña* in his closing lesson of a series of conferences on Meteoropathology, which we organised last Winter, had more to do with agronomy than with medicine.

Here we might answer in the same way as when we were asked what life is, that "if I am not asked, I know, but if I am asked, I do not know".

Keeping to the task in hand, to see if we can explain by what intricate mechanism the weather acts upon us, it would take too long to discuss all the theories formulated to give a satisfactory explanation of the way a climatic complex acts upon us.

In virtue of the modern, suggestive and attractive theory we shall give only by way of a summary the opinion of a well-known physician who latterly has devoted himself with real ardour and tenacity to the study of the mechanism by which the action of the weather might be explained; we refer to the works of *Manfred Curry* and his school who in Riederau (Germany) has established a centre of bioclimatic studies the result of which is the extensive treatise on *Bioclimatica*, published in 1946.

Dr. Curry explains in his book that he became interested in these kind of studies simply because he himself was meteoropathic. Dr. Curry passed really anxious periods, waiting for the barometric oscillations of the apparatus he had installed at his bed-head, when he came to the conclusion that his trouble was really on a par with the barometric rise and fall, in the course of the days as well as of the seasons. With the help of the so-called climatic cameras, in which varied conditions of pressure, temperature and damp are artificially created, he began to study systematically which of the meteorologic factors the reappearance of his trouble might be due to. These studies carried on together with eminent physicists, went from failure to failure, becoming interested again by the study of the influence of the electric charge in the atmosphere by means of the so-called "farady cages". However the hopes formed at the beginning soon disappeared and the wish of the investigators to study fell to such a degree that they were on the point of abandoning any new attempt or kind of trial. Anyway, before doing so, they decided on one last trial to see whether the cause resided, not in the physical agents observed until then, but perhaps rather in the chemical composition of the atmosphere, which is clearly likewise susceptible to variation under the influence of storms, thunderstorms, etc.

The stability and slight variation of certain chemical elements of the air being known, such as nitrogen and other inert gases like Argon, xenon, etc., the investigator devoted himself to the study of these chemical components which are known to have considerable variations, like ammonia, chlorine, nitric oxide, radon, iodine and ozone. Of all these, only ozone showed a certain dependence of superior animal life. What is more, there exist in the air certain active forms of oxygen which are called "ozonides" and to which Curry has given the name of "aran". This inodorous ozone, more stable than that generally found in small particles of the atmosphere, becomes introduced in to the smallest part of the bronchial tubes and lungs and from there acts upon the entire organism. Complicated photo-electric registering ap-

paratus permit to-day the observation of these "ozonides" so that already enough is known for some conclusions and observations to be established. The most important of these are:—

- 1° Their quantity varies by day and by night.
- 2° Meteorological factors and changes in the weather also cause variations.
- 3° Oscillations occur according to the season.
- 4° North winds bring about a considerable concentration whilst there is little effect with South winds.
- 5° The so-called cold winds are also accompanied by high values whilst warm winds show low values.
- 6° Their concentration varies with their height above sealevel.
- 7° A very high value is reached some moments before the beginning of a thunderstorm and these values drop once the storm has started.
- 8° Their concentration is low in closed premises, industrial cities with fog and lack of winds.

Although it has not yet been possible to produce aran gas synthetically, the physiological action of similar products has been studied and it is known that their lack produces symptoms as of hyperactivity of the sympathetic nervous system (tachycardia, hypertermia, increase of basic metabolism, peripheral vasodilatation, etc.). On the other hand by breathing high values of aran, vagotonia is produced (bradycardia, hypotension, hypotermia, lowering of metabolism etc.).

Studying the psysiological action of aran upon a great number of individuals, *M. Curry* observed that there exist two groups responding in a very distinct way to the lack or excess of this gas. These two great groups, which *Curry* has come to call group C and F, form the terminology of a new constitutional typology which we might call "meteoropathic typology of *Curry*", one more of the many existing in the science of constitution.

We shall leave on one side the features of each one of these groups, as from the descriptions given by him it is perfectly clear that type C is but the picnic type of *Kretschmer*, the brevilinear type of *Pende* or the vagotonic one of the French authors, or whatever one might like to call it, on the other hand, type F is the leptosomatic one of *Kretschmer*, the longilinear one of *Pende* or the well-known sympathico-tonic type.

When the concentration of aran gas is low the patient shows no discomfort at all but responds to diseases of the spasmodic type when

the concentration of aran gas become high. On the contrary, individuals of type C become ill with inflammatory symptoms when the value of aran gas falls excessively. One and the same disease like tuberculosis acquires in one or other individual entirely different characteristics. In the same way bronchial asthma is predominantly spasmodic in type F, being on the other hand more inflammatory in type C. By way of summary, the following scheme may be established:—

<i>Decrease of aran</i>	<i>Increase of aran</i>
With South wind	With North wind
At night and early morning	By day
In a low altitude	In a high altitude
With hot weather, mist	With cold front
With hot front	This increase of aran
This decrease of aran produces	produces Vagotonia
Sympathicotonia	Produces discomfort in types F
Produces discomfort in types C	No discomfort in types C
No discomfort in types F	

The asthmatic individual of type F becomes worse when aran gas increases in the atmosphere, which speaking meteorologically would be when north winds are blowing, on account of the presence of cold winds, at a height or during the day. On the other hand the asthmatic individual of type C gets worse when the values of aran are low, which occurs in exactly opposite meteorological conditions, that is to say, when South winds are blowing and warm fronts establish themselves, at night and in places a little above sea level.

Do things really occur in the sense defended by *Manfred Curry*? The studies of typology initiated in our service and continued in our Institute by *Ferrer Hombrevella* and *L. Pau-Roca* permit us to assure that with reference to our country, the proportion of asthma of type F is very much greater than that of type C.

A classification of asthma in two parts is not new.

Floyer in the XVIIth century already established two great groups of asthma which he named convulsive and continuous. Later on *Cullen*, *Willis* and many others continue to admit these great groups of asthma in spite of modifying the terminology. Recently *Unger* has also proposed the classification of asthmatic individuals into a group of paroxysms and of chronic ones, which we agreed upon to call dry and humid ones.

Keeping to what has been suggested by *Curry* respecting improve-

ment or aggravation of asthma through meteorological changes and in the last place subject to various of aran, it should be noted that the majority of our asthmatic patients that are predominantly of type F ought to get worse in the presence of a cold front or when north winrs are blowing, when they go higher or during the day. And this we see occurring in a completely opposite sense to the one stated, that is to say, this group of asthmatic patients become worse in the South wind when warm fronts are established or at night or remain in low lying places.

Given the impossibility of realising for the moment any technical or direct measurements of aran to throw light upon what occurs in our climate, apparently in contradiction to *Curry's* observations, there is for the moment nothing left but to make a superficial study of the meteorological conditions reigning in our region whereby we shall know indirectly the possible oscillations of aran.

As we have already stated, *Curry* and his school have made known the meteorological conditions governing the variations of aran. Referring only to our East coast it should be deduced from the usual climatic conditions that there should be high values of aran during the months of December and January when high pressures are prevalent in our peninsula and also during the daytime when North winds are blowing. The quantity of aran should undergo considerable oscillation in Spring and in Autumn.

A new revision of our clinical material, now carried out with a view to knowing in a general way which are the times of aggravation and of well-being among the to great groups of asthmatic individuals, clearly show that for the asthmatic patient there exist in the course of the year two times which are really prejudicial to asthma and these alternate with two periods of relative improvement if not absolute calm.

The times of the year when the asthmatic patient feels worse are Spring and Autumn whilst in the height of Winter (December and January) and during Summer he feels free from discomfort and aggravation.

If about 80 % of our asthmatic patients belong to type F and these improve precisely in those months of supposed maximum concentration of aran gas, when in reality they should become worse, there is something which for the moment escapes our comprehension and might be the subject of future investigations.

This group of asthmatic patients do not become worse when re-

moved to higher climates, the opposite occurs; nor are they worse during day-time when the quantity of aran gas is raised as it is at night and seecially in the early morning when their discomfort is accentuated. And finally, the times of aggravation are precisely those when aran gas is neither high nor low, but when its instability and great variation of contents predominate. (Changeable weather in Spring and Autumn).

From what has been said we may deduce that the aggravation or improvement of asthmatic patients, more than being conditioned by a greater or lesser quantity of aran or a greater or lesser faculty of reactioning of the organism, has to do with the instability or variability, which in a more ample sense we know to be the factor in the appearance of the asthmatic crisis.

We are foremost in regretting that these statements deduced in the light of the clinic and in an indirect manner, could not be accompanied by an experimental part, that is to say, by systematic measurement of aran gas with *Curry's* apparatus. Nor do we pretend to under-rate the extensive, really titanic work performed by *Curry* and his collaborators and much less would we dare to qualify the above remarks as a criticism of their work; we have no intention of doing so, and as we have already stated at the outset, the originality and suggestion of the theory and the fruitful camp for study are on the whole what has induced us to mention the matter extensively.

A new impetus has been to Bioclimatica by *Selye* and his school who take into consideration the factors generally studied in meteorology, such as cold, solar radiation and barometric pressure, that currently cause the appearance of what is known under the term "general" syndrome of adaptation".

All these agents understood together as "alarming stimuli" produce hypertrophy of the suprarenal cortex, an evident sign of the response of this special gland to general syndrome of adaptation.

The part played by the suprarenal medulla in relation to its adaptation to cold has been extensively studied by *W. B. Cannon*. It is very possible that the other cosmo-climatic components that act upon the organism do so also through the glandular apparatus of adaptation.

The primitive schemes of *Selye* spoke of an unknown way acting as a bridge of union between the "alarming stimuli" and the suprarenal cortex. In virtue of the works of *Long* and *Fry*, *Vogt*, *Sayers*, *Morros Sarda*, etc., we now that the mediator or bridge of union is epinephrine.

Actual investigations carried out by ourselves show us that an important part in this bridge of union is played by the adrenergic mediator sympatine which by itself and in an analogous way would stimulate the reserves of adrenocorticotrophic hormone and those of the suprarenal cortex.

In this order of ideas we may presume, without wishing to speak the last word on it, that the action of certain meteorologic agents be explained as acting in the organism through the mechanism of S.G.A.

As we consider that allergy is but a chapter of this extensive general syndrome of adaptation, everything we may bring up in favour of an explanation of the mechanism of allergenous action on the allergic individual will be valid for the explanation not only of the S.G.A. but also to what makes reference to the mechanism of the action of meteorologic factors upon an allergic patient.

Accepting antigen as an "alarming stimuli", we have also attempted to find out which is the bridge of union between its direct action and the glandular response. Other authors like *Aguirre* and *Arjona* have tried to get to know whether in allergy there exists or not a glandular response of an analogous type to that obtained in the S.G.A. and of the negative results of their conclusions we shall speak later on.

Experimental part: The Part of the Adrenergic System in the S. G. A.

Starting from the basis of there existing a previous adrenergic mechanism in the development of any crisis of allergy, there still had to be found out whether an analogous mechanism existed for normal organisms submitted to the action of one of the meteorologic agents. Cold was the easiest to produce and our experiments were based from it.

So as not to incur in repetition in these lines and considering that the result of a first group of investigations has already been published (*Annals of Allergy*, vol. 7, page 46-59), 1949; *Acta Allergologica* vol. 3, page 20-25, 1950; *Acta Allergologica* vol. 3, page 12-19, 1950; *Acta Allergologica* vol. 3, page 215-226, 1950) we shall mention only the conclusions led to in the last named (*Acta Allergologica* vol. 3, page 215-226, 1950) and those recently reached and still unpublished.

1a It has been amply shown by us that during anaphylactic shock in the dog there exists an important overproduction of sympatine, the values of which oscillated between 3 and 15 times more than the initial ones (with an average of 5.5 times more).

2a There remained to be found out whether these increases in sympatin were secondary to those of histamine or whether on the contrary they constituted a previous link in the chain of histaminic liberation or of substances similar to histamine. This special point has been resolved by means of an extensive series of experiments in rabbits. This animal is known not to liberate any histamine in anaphylactic shock, when it was observed that the values varied between 2.7 gammas % c. c. of blood before the shock and 8.0 c. c. % after same.

In this group of experiments is clearly demonstrated the fundamental importance of the adrenergic system acquired in the elucidation of allergic phenomena. Experimental data was given for a series of suppositions and hypotheses presented in the year 1934 and which was the basis for the publication in the *Rev. Esp. de Medicina y Cirugia* under the title of "On the supposed Vagotony of asthmatic patients" (A new pathogenic conception of asthma).

A second series of experiments has been carried out in 10 dogs, in which the quantity of sympatine in the blood was determined before hand and after a stay in a freezing chamber during 6 hours at a temperature of 5 degrees C. above zero.

The results of the mentioned experiments are given in the following table.

TABLE I.
Quantity of sympatine in the blood of dogs after the action of cold.

1.	2.	3.
1	0.5	3.7
2	0.6	4.2
3	0.8	2.7
4	0.6	2.3
5	1.2	5.8
6	0.35	9.0
7	1.0	5.0
8	0.2	1.8
9	0.7	3.2
10	1.1	4.8

1° Number of experiment.

2° Quantity of sympatine in gammas per 100 c. c. of blood before cold.

3° Quantity of sympatine in gammas per 100 c. c. of blood after cold.

Conclusions.

We would insist once more that in all our experiments we do not pretend to consider as closed the physiopathogenic mechanism of the

response of the organism in relation to meteorologic factors. We only pretend here to give a possible explanation to the mechanism of action of but one of the meteorologic factors, which is the cold.

This action would follow the same way as that of antigene acting upon the allergic organism, that is to say by mobilising the adrenergic system at a previous stage or of pre-shock study. Although the S.G.A. and allergy begin along a common route of adrenergic response the further progress of the response in the S.G.A. is by phases more advanced than that of simple mobilisation of epinephrine and sympatine.

In anaphylactic shock, possibly due to the "size" of the injury or for other reasons, the phenomenon would not reach these stages of hormonal mobilisation, things would only remain in the stage of the adrenergic mobilisation without participation of the suprarenal cortex.

The protection of the anaphylactic shock would come about by this previous adrenergic phase, which would confer upon the organism an immediate protection, whilst the liberation of corticoides, not demonstrated in the anaphylactic shock would give the organism a more lasting protection.

In other words, the acuteness of the anaphylactic phenomenon would require from the organism a mechanism of rapid defence. It does this by producing adrenalin and sympatine. The chronic condition of the phenomenon of the S.G.A. would make it necessary that apart from the immediate response of the adrenergic system, other defensive systems of action are perhaps neither so rapid or so intense, but of a rather more lasting and sustained effect.

Following this line of argument it is possible to understand that given the parallelism existing between the adrenergic response of current antigene and allergic subjects, and the cold meteorological factor in normal subjects, the same results may be produced by interpolating one or another of these factors, a conclusion which would lead from a physical allergy to a physical action without allergy.

2^e Sujet Principal – 2nd Main Topic – 2 Hauptthema

ALLERGIC PERSONALITY

By

E. ORTIZ DE LANDAZURI, M. ROJO SIERRA, L. RUIZ VIEDMA,
E. JIMENEZ MOLINA, A. ORTIZ RUIZ and J. NUNEZ CARRIL

In order to study the possible existence of an allergic personality, we have to examine the hereditary, constitutional, psychic and re-

actional features of allergic patients. On one hand we should be able to foresee the possible origins of allergic disorders and on the other predict how serious they are. According to Jimenez Diaz allergy is something more than a simple antigen antibody reaction: it shows a certain individual deviation of the reactive capacity. The allergic patient is ready to subject himself to all kinds of questions and test. We realize the intensity of the affection by the readiness and facility with which the patient submits physical and psychic data to our investigation. Frequently a general conversation with an allergic patient throws more light on his disorders, even without speaking about them, than any other investigation of his sensitiveness.

We should ask ourselves, a Rackemann points out "is this a true personality or is it only the consequence of the reiteration of allergic symptoms?" The purpose of this present study is mainly to answer this question.

We analyzed 300 bronchial asthmatic patients and this provided us with data about the uniformity of the evolution of allergic phenomena. Our results on the influence of sex, age at onset of the disorders, characteristics of the asthma and etiological influences, coincide with those of other authors. We completely agree with Eriksson Lihr on the age of onset of the disorders, which starts at school-age in the case of girls and, in that of boys, in the earliest years of life.

The human personality has to be studied in its entirety: from the highest activities down to its cellular structures. "Life as a whole, writes Zubiri, is based on the most elementary activities. "Thus we must study the allergic personality through: a) the autonomic nervous system, b) the H substance, c) the cellular and hormonal mechanisms and d) the psychosomatic aspects. In the so-called allergic personality, the link between the psychological and somatic constitution has to be the intermediary brain, as White recently pointed out.

Our aim is to give norms for the clinical investigation of allergic patients, in order to be able to study the deviation of the reaction in the allergic personality, which Jimenez Diaz has called the "disreactive nodule". As Russel pointed out, we must change the concept of the "organs of allergy" to "allergy of the whole personality". Vasomotor lability, according to Francis, is the most characteristic stigma of this personality.

In the allergic disorders, the study of inheritance shows how a special disposition is inherited, but not a special sensitiveness, which in both cases shows itself as asthma, in others as urticaria or eczema,

or even as some of these symptoms together. We obtained these data from 300 asthmatic patients, 50 % of whom had a hereditary basis.

Infection comes first among the peristatic factors in the etiology of allergic disorders. We completely agree with the opinion of Pasteur Vallery-Radot, "Il ne s'agit plus de reaction allergique a un microbe mais des maladies allergiques provoques par un microbe." We accept for some cases bacterial allergenic asthma, as Jimenez Diaz does, though in other cases bacterial asthma may come under the classification of intrinsic asthma, as Rackemann suggests.

According to the Stromgren index, allergy affects a higher average of picnic women and of asthenic men.

The study of some somatic aspects of the allergic personality gave evidence of an excess of dermographism and sudoration and likewise, during the asthmatic attack of an increase of histamine in the excreta. The results of the first Robinson-Power test are more frequently pathological in allergic patients. The second Robinson-Power test does not have any practical value, because it gives the same results in normal and allergic patients.

There was no difference in the febrile reaction after the injection of 0.1 ml. of T.A.B. vaccine. We have not found in allergic patients any variation in the modification of the blood sugar curve after insulin and adrenaline injection, as compared with normal persons. The capillary study was negative.

The patient's psychobiography should be studied by personal contact, considering specially these features: attachment to the mother, passive character, compulsive humour, realism, reproductive mind, lively expression and great emotivity.

Attachment to the mother: French and Alexander were the first to point out the existence of a strained fear towards the mother in asthmatic patients studied psychoanalytically. They are very anxious to avoid thoughts or feelings that could offend her. With the attachment to the mother is frequently connected a sense of helplessness and a fear of being alone. This vital dependence does not reach an obsessive stage.

The compulsive humour, so frequent in allergic persons, is situated between the less serious phenomena of fixed ideas and the anacastic personality. So that the compulsive humour could be considered as a sublatent anacastic personality and therefore cannot be considered psychopathic. Individualism, perseverance, the faculty of organising, good taste and skill in hand-work are often present in the allergic

patient as a consequence of this compulsive humour. This sense of order is not a virtue but a necessity to avoid anxiety produced by the allergic disorders. For instance, a twisted picture produces anxiety, because the patient has "a compulsive humour for order."

Allergic patients are realists. They adapt themselves to their surroundings. They feel sure of themselves. Nevertheless we cannot consider this realism as materialistic.

These patients are passive because they need the feeling of being guided in order to avoid responsibility.

Reproductive intelligence: it flows from passivity and compulsive humour.

Sense of perception: speaking with allergic patients two facts call our attention, on one hand their quick comprehension, on the other the exactness of their answers.

The allergic patient is fluent in his speech and lively in his expression. These characteristics were always studied in comparison with the reactions of normal individuals.

It seems to us that the psychic aspects of the allergic patient are not merely a reaction to their somatic troubles, but that both psychic and somatic phenomena are complementary. They have in common a slight degree of immaturity. The psychic features may be spotted even before the manifestation of 11 allergic symptoms.

We also believe in the existence of potentially allergic patients who, without having any of the external symptoms, show the psychic characteristics stated above. A study of their background reveals that allergy runs through the family.

3^{me} Sujet Principal – 3th Main Topic – 3^{te} Hauptthema

URTICARIA AND ANGIO-NEUROTIC OEDEMA

By

R. FROUCHTMAN, M.D.

This report is based on the study and revision of 202 cases of urticaria and angio-neurotic-oedema of the recurring type. 59 are males and 143 females.

On revising the histopathology the differences existing when the papules have made their appearance are noted, although usually the

histologically structure is similar in contrast to the marked variety of the clinical picture.

The report describes the urticarial eruption which is always due to an anatomico-functional reaction of the capillary system which is common to all kinds of urticaria. The histamine theory is also revised as being more usually accepted although the majority of reports tend to show that histamine or some other similar substance intervenes as a cause of the urticaria. However there are still many aspects which remain uncertain and it seems probable that other active substances than histamine take part in these phenomenon, though so far our knowledge is insufficient to describe the ultimate cause of the urticarial swelling.

Furthermore it must be mentioned that urticarial patients have a special personality which show in many vegetative symptoms which appear with, before and after the urticaria. It is to be noted that in patients affected by this disease of great importance is their constitutional disposition to allergy, often inherited, which is fundamentally characterised by an abnormal reaction which may be accelerated by different mechanisms of which one is the shock antigen-antibody. For this reason it is useless to classify urticaria into atopic and non-atopic as there is no other difference between urticaria and a reagenic oedema than that of specific sensitivity.

There follows the study of the different etiopathogenic symptoms and factors which were summarised in a series of tables in which the allergic constitution and background of the patient and the relevant presence of many disreactive symptoms of a typical vascular mechanism are shown. Symptoms of headache, and less frequently asthma, angio-neurosis which is a recurring symptom, choking, itching, giddiness and headache are all found. The high rate (74 to 78 %) of allergic inheritance is noted, as well as poliparental inheritance usually of headache and several cases of urticaria and oedema recurring through several generations.

Between the ages of 15 and 40 years popular urticaria is most common. Also considered in the report is the influence of endocrine dysfunction, whatever its cause, the influence of menstruation and the psychogenic influences commonly found in hysterical patients.

After classifying the urticarias by their morphology, localisation and rhythm, the symptomatology of these syndromes and other recurring symptoms which are present in 93.5 % of the cases is studied. These characteristics are of a functional and revertible character. They

may appear before, after or at the same time as the urticaria but frequently disappear on removing its cause. The patient must state if these symptoms come separately and on what occasions as they may lead to a wrong diagnosis, as both may be caused by allergy. Among the urticaria equivalents must be mentioned because of their frequency, asthenia, dizziness, or sickness, loss of voice, rheumatic symptoms and pain in the hepatic region and also paroxysmal constipation, glossitis, etc.

Investigations required are:—capillary resistance which is generally weakened, eosinophilia, arterial pressure, leukocytes, which generally fall on appearance of the urticaria, calcemia and potasemia are normal when investigated. Blood proteins independent to the eruption are very little altered but due to a protein imbalance the albumin-globulin ratio is either lowered or inverted during an attack.

A special chapter deals with clinical differences that have to be considered between the oedematous dermatographic, physical and factitious urticarias and those skin reactions among which there probably exist a physio-pathological analogy but due to different conditions do not show the same characteristics.

Attempting to classify the etiological causes helps but little in the diagnosis as it must be noted that in recurring urticarias there is never only one cause. In many cases, even in the physical forms, the etiopathologic study signals out other determining factors whose action is conditioned or added to the apparent cause; in these cases the eruption follows all or any stimulus whatever the causal mechanism. Nevertheless often there does exist one fundamental factor responsible for the urticaria though this is helped or conditioned by other agents, and for this reason the 202 patients have been classified into different etiological types: *Food* (12.8 %), *Infection* (11.3 %) possibly due to a dental, tonsillar, sinus or intestinal focus (many of them are sensitive to Aspirin); *Infestation* (0.49 %), *Drug* (0.99 %), this includes many different drugs, *Hepatobilia* (11.3 %), *Gastro-Intestinal* (0.45 %), *Physical* (7.3 %) caused by mechanical agents such as cold, exertion, heat and sun and in some of these cases passive transfer of antibodies is possible. Finally a large group due to *Inhalant*, *Psychogenic*, *Contact* and *Complex* causes. These represent cases resistant to treatment, often due to more than one cause, all of which must be treated at the same time to obtain good results. There are, however, 30.6 % of cases whose etiology is only partly known or no known cause can be found.

Finally is considered the differential diagnosis between urticaria

and angio-neurotic-oedema. It is suggested that three different lines of therapy are followed—symptomatic, etiologic and, on the chronic types, non-specific treatment.

THE GASTRO-INTESTINAL ALLERGY BORDERLANDS EMPHASIZING THE ALIMENTARY HEMOLYSIS SYNDROME*

By

R. SURINYACH**

Bacteria, drugs and foods are the main sources of gastro-intestinal allergy¹. But here these agents act frequently within a band badly defined between allergy and toxicity.

We will now examine some aspects of these limiting zone in each of the three groups separately, emphasizing the Alimentary Hemolysis Syndrome.

In order to accept a syndrome as allergic-according to the Doerr boundary principles, it must possess the following conditions:

- (1) aberrance from the norm,
- (2) specificity with respect to the provoking agent,
- (3) clinical symptomatology independent from the pharmacodynamic properties of the agent, and
- (4) identification of specific antibodies.

From the point of view of separating allergy from toxicity, number (3) above is fundamental, namely, the independence and variability of the reaction. The deviation from the norm, number (1) above, can be mistaken with the special susceptibility, or also with the special resistance to be seen in certain individuals towards determined toxins. In some of these cases there also exists a form of specificity which makes point (2) above, hardly distinctive. Finally, there are very well known

* This is a summary of the more original part of a 75 pages report "Alergias Digestivas read before the second Spanish Allergy Congress, held in Sevilla, on October 20, 1951.

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¹ The parasites infesting the digestive tube in Spain, provoke general, rather than local, allergic syndromes.

zones within allergy where the demonstration of antibodies is not possible; whether this is due to technical difficulties, or perhaps due to dealing with forms that are immunologically immature, it is obvious that the demonstration of antibodies cannot be utilized as distinctive in all cases. Therefore, the principal distinctive sign used in practice to classify an action as toxic, is when it reproduces in a fixed manner its toxicodynamic clinical picture, or any similar one. Whereas, the principal distinctive sign of allergenic action is the production of reactions characteristic of the allergic shock organs. Allergic reactions will only develop regularly if the shock organ is determined by a special method of contact peculiar to the substance.

The human anaphylactic shock pictures—only occasionally seen—are slightly more varied than those of the experimental anaphylaxis on any of the animal species. They are, anyhow, less varied than the pictures admitted in human allergy. Regarding the number of human shock organs our knowledge is still limited.

Bacteria

The relation of Sanarelli-Shwartzmann phenomenon with allergy comes under consideration in spite of its lack of specificity. Recent investigations have demonstrated that this phenomenon is inhibited by the nitrogenated mustards, the ACTH, the Cortisone, and partly by the antihistaminics. Between the Sanarelli-Shwartzmann phenomenon and atopic allergy, there seems to exist an imperceptible transition. *Bordet* set the tuberculous reaction at the center point of this band, the first part of which has been designated by *Gracian* with the very graphic name of *topotoxy*.

Drugs

So that the action of a drug can be considered as allergenic, it is necessary that it provokes a reaction different from its pharmacodynamic properties. This is indispensable, inasmuch as the allergies of this group offer a particularly poor immunologic picture.

Nevertheless, it occurs that some drugs provoke syndromes which, although different from their pharmacodynamics, are extraordinarily fixed. This leads one to believe that the conjugates, formed by the drug acting as hapten, maintain the remnants of the previous toxicity, or possibly they acquire a new and unknown form of toxicity liable to be taken as allergy.

Foods

Quite a long time ago we demonstrated (*Westphal* and *Surinyach*, 1933) that the introduction of a allergen into the stomach of patients with gastric allergy, provoked a great elevation and lengthening of the free acidity curve. This form of reaction entirely coincides with physiopathological changes as observed by other authors through the use of allergenic contrast medium, or through the introduction of the allergen under gastroscopic observation.

Although we possess clear examples of gastro-intestinal segmentary allergies produced through the hematic system, in the majority of our cases, as occurred with those of *Pollard* and *Stuart*, it seemed to be a matter of local allergy. The entrance of the allergen seemed to sensitize by mucous or epimucous contact.

On the contrary, some alimentary allergies do not appear as produced by a shock organ in the neighborhood of the contact tissue. The allergen enters through the gastro-intestinal tract, but the reaction appears in the bronchial or in the skin. Among these alimentary actions, some attracted our attention due to their strange fixness.

With extraordinary and suspicious frequency, strawberries provoke urticaria, chocolate provokes headache, and fava beans hemolysis. It is not our intention to deny that there exists, for example, an allergic urticaria to strawberries; on the contrary, we could cite fully demonstrative cases. What we desire to point out is that strawberries must contain something capable of producing symptoms in such a constant manner toward an organ territorially separated, as the skin is, and toward a syndrome as urticaria. This something we must theoretically consider as a form of toxicity, whether or not it coincides with an allergic sensitivity.

We have not had the opportunity deeply to investigate what for the present we shall call "the clinical picture of strawberries" and "the clinical picture of chocolate". Nevertheless, we can supply original knowledge regarding the hemolysis provoked not only by fava beans, but by a whole group of foods.

The Alimentary Hemolysis Syndrome

It has been known for some time that in certain nucleus of population around the Mediterranean, there exist individuals who suffer from hemolysis when eating fava beans. The disease is also very interesting in the genetic and hematic aspects, but we will now only refer to its relations with allergy.

The patients affected by favism, eat fava beans and a few hours later begin into fever, nausea, vomiting, vertigo, abdominal distention and pain—and later: hemoglobinuria, depression and icterus. The hemolysis can produce acute anemia below one million red cells per cubic millimeter. Some cases end in death through collapse or with nephritis and uremia. Two days later, the majority of patients start making red cells and full recovery occurs in few weeks. Other less serious cases only feel indisposition, darkening of urine and slight icterus, and, in some cases, not even this. A curious aspect of the disease is when the symptoms appear in some individuals—although in a more sudden and attenuated manner—when coming near a flowering fava beans plantation.

In 1921, *Pesci* issued the hypothesis that favism could be an allergic disease. This hypothesis at first sight seems logical, inasmuch as other individuals eat fava beans at the same table with the patient without experiencing the least indisposition, and also there occurs the apparent analogy between the inhalatory forms of favism and pollinosis. The fact of hemolysis was at first interpreted as an exaggeration of a phenomenon which would be outlined in the experimental anaphylaxis; later there appeared more complicated interpretations.

Since *Pesci*, the allergic interpretation has been accepted by almost all the authors and it so appears in the recent treatises that mention favism. Statistics of cutaneous proofs and passive transference have been supplied to the point of rendering it somewhat difficult for us to adopt an objective position from the start.

Nevertheless, when we published in Barcelona (*Pedro Pons & Surinyach*, 1950) the first cases observed in Spain, we were non-committal regarding the relations between favism and allergy.

Observing the patients from the point of view of allergy, the author was surprised to find none presenting family or individual allergic history. Neither did they present any constitutional aspect capable of making one think on allergic personality. All patients seemed intoxicated after ingesting fava beans. Some time later, when the author discovered a very important source in Menorca, Balearic Is. (with a 2 % of all the population in the western part of the island affected) he did not see there the same cases of toxic and sporadic aspect as in Barcelona. In Menorca the patients appeared united by strong bonds of endogamy and many of them became ill merely on approaching flowering fava bean plants, something we had only read about until then. The latter patients gave much more the impression of being allergics.

We soon got the intuition that for favism to exist in our country it is essential to have the joint presence of these two factors: (a) endogamy and (b) cultivation of fava beans in the locality. The endogamy centers thrive economically isolated and therefore, do not usually import fresh vegetables for their support.

The author has helped to enlarge the etiologic base of favism. New sources of hemolysis have been found in the year 1951, over the same groups of individuals who present hemolysis due to fava beans: through peas (*Marcolongo*, followed by *Surinyach*) through beans (*Surinyach*) through pomegranate and vetch (*Marcolongo*) and through prickly pear (*Surinyach*).

Pathologically we believe to have demonstrated that the fundamental cause is from ingestion and not inhalation. All our patients who produced hemolysis by inhalation also produced by ingestion, but not vice versa.

The cutaneous sensitivity of patients in front of fava beans has been examined by the author in the following manner:

Recently obtained juice of tender fava beans, was Seitz sterilized, dialyzed and stabilized with 50 % glycerine. In 32 patients scratch test hypersensitiveness was not demonstrated. In a hospitalized patient we employed intracutaneous tests at progressive concentrations up to 1/100 of this same juice and also scratch and ophthalmic tests with dry pollen of fava beans; negative results. Consequently, we have not carried out the passive transfer test, and we doubt the interpretation of those made by other authors.

There still was one aspect in favor of the allergic interpretation: the generally accepted clinical sensitivity of these patients to the inhalation of *Vicia faba* pollen. The author's investigations showed that the inhalatory syndromes are produced not only in the proximity of flowering fava bean plantations, as described in books, but also: in the fava beans storages, when threshing the grain from the stock, and at home on cooking the grain. These are conditions wherein pollen intervention can be eliminated. Undoubtedly, the inhalation forms are due to a susceptibility to volatile oils not only present in the flower, but also in other parts of the plant. It is a *Vicia faba osmyls susceptibility*.

After establishing a multiple etiology and the now changed pathology, the author prefers to substitute the historic designation of "favism" to that of: "Alimentary Hemolysis Syndrome". This expresses with better precision and without conventionalism the new meaning of the disease.

It suggests that some legumes have a toxin, which varies according to the species, to the varieties, and even according to the harvests. It is probable that it deals with the hemagglutinins already employed in veterinary serology and whose pathological significance was noted by *Landsteiner*. In our opinion there exist individuals constitutionally endowed with a susceptibility to the toxin. We find them grouped in families distributed predominantly around the Mediterranean sea. When endogamy and other causes are present, a centre of disease may be formed.

When eating a lot of toxin haemolysis may affect individuals with low grade susceptibility. In cases of less toxic absorption (as always occurs in inhalation forms) a great susceptibility to the toxin is necessary and even then, the symptoms are milder.

The author has described a masked form of Alimentary Hemolysis Syndrome combined with Cholelithiasis. It deals with patients in whom the yearly repetition of hemolysis provokes the formation of true gall bladder stones. These produce a symptomatology capable of causing confusion.

We consider that the Alimentary Hemolysis Syndrome should be removed from the field of allergy and transferred to the limited field of toxin susceptibility.

It is not possible to ascertain whether or not under very extraordinary conditions the toxin may be antigenized and the Alimentary Hemolysis Syndrome produced by an allergic mechanism. This was the author's former and still undemonstrated *dualist theory*.

From Toxicity to Allergy

As already stated, we have arrived at the point of view that many substances before acting as allergens began to provoke one or other method of irritation. The quality, quantity or manner of contacting the substances, are capable of exciting; and it may sometimes occur that the excitement is conditioned to an individual, who is not allergically susceptible. In as much in this respect excitement and toxicity become similar, slightly toxic yet selective forms follow immunological laws than the laws of chemistry and arithmetic which apply to toxins.

A toxin can be made through conjugation an antigen (hapten) which we believe represents the acquisition of new properties, but not necessarily the loss of the old ones. In this sense, toxic and allergenic actions could co-exist or combine in the same substance. We are also inclined to admit the existence of intermediate and unknown forms of

patients' reaction situated between toxicity and allergy. Many of the clinical forms which have, the immunological characteristics of allergy.

It is very useful to start with a clear distinction between the concepts of toxicity and the allergy, but as extreme ends of a same band.

Sujets divers – Other Topics – Andere Themen

ACTH AND CORTISONE IN THE TREATMENT OF ALLERGIES¹

By

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So much has been written about the chemistry, physiology, pathophysiology, and the mechanism of action of Adrenocorticotrophic Hormone (ACTH) and Cortisone (Compound E), that it is probably unnecessary to review preliminary considerations of them. The subject matter of this paper, therefore, will be limited to a clinical evaluation of these two hormones in the treatment of allergies. Though of different origin and structure, Cortisone and ACTH have similar if not identical effects on the nonhormonal diseases.

Some of the most dramatic results of ACTH treatment, and those of Cortisone, lie in the field of allergy. Sufficient clinical reports have been published to evaluate their indications for use in allergic states to now conclude that these hormones have been shown to have great therapeutic effect in the temporary suppression of symptoms in the various allergic diseases, such as bronchial asthma, allergic rhinitis, allergic dermatitis, urticaria, and drug allergy. It must be stressed at the onset that the effect of these drugs in allergic diseases is only *temporary* and *not curative*. They do not replace the need for the usual allergic management. The numerous side-effects, some very alarming, must be detected as early as possible; which requires close observation of the metabolic state of the patient.

Since these hormones do not remove the underlying basic factors, we do not know how they act. When they are withdrawn from the patient the symptoms return, usually promptly, but may be delayed for

¹ Read before the second meeting of the "Spanish Society of Allergy".

longer times. At the onset, the most enthusiastic reports were based on the dramatic results obtained from its first use only. However, with return of symptoms after a period of remission, these hormones frequently made the patients worse, and some patients died of extreme exhaustion. Many physicians who had these hormones readily available for use could not have fully realized the dangers of interfering drastically with the body's physiological processes. Distressing untoward reactions of Cortisone and ACTH may be: an abnormal effect on the glands of internal secretion, the production of Cushing's syndrome, depression of gonadal function with its numerous attending symptoms, and effect on the electrolytes, cardiovascular system, lowering resistance to infection, a marked muscular weakness, osteoporosis; changes in the skin, subcutaneous tissues and mucous membranes; changes of the central nervous system with resultant psychotic reactions; or the production of ulcerations in the gastro-intestinal tract. A better understanding of these untoward reactions has resulted in a more conservative use of these hormones, particularly in the allergic states.

Hormone therapy should be tried in those patients where immunization and other protective measures have failed for over a year. Patients with severe status asthmaticus who do not respond to the orthodox procedures are treated 4-7 days with ACTH, depending upon the stage and severity of the case. ACTH is given intramuscularly or intravenously, with a total of 80-100 mg. daily, given in *divided doses* at intervals of six hours, and then followed by diminishing amounts and intervals. The aim is to obtain a low continuous effect by giving 10 to 20 mg. of ACTH in 500-1000 cc., in 5 % glucose solution, at a comparatively slow rate. Doses as low as 2-5 mg. can be given if the patient's symptoms subside.

This low dosage schedule of 100 mg. of ACTH in 24 hours in *divided doses* results in very few complications, which is usually a temporary psychotic reaction. Some patients may develop edema and potassium depletion. When administering these hormones, the urine and blood pressure are carefully watched, since glycosuria may result. Therefore, potassium salts should be used in conjunction with the administration; potassium iodide 2 grams, or potassium chloride 1-2 grams, in divided doses.

The return to normal of the blood sedimentation rate, and reduction of eosinophils to normal *do not determine* whether sufficient amount of hormones has been given, so they must be administered with due caution and care.

Both hormones have a place in the treatment of vasospastic rhinitis with polypi and with chronic urticaria. Recovery in nonseasonal rhinitis can be accelerated, particularly in those cases where it has been impossible to determine the etiological factor, if the patient is placed in a hospital and given ACTH or Cortisone. ACTH lowers the patient's resistance to infection, and should never be used in the treatment of tuberculosis. Thromboses may also result. Small doses of ACTH do not cause adrenal cortex degeneration in the treatment of allergic dermatoses. Larger doses seem to have to be employed than used for respiratory allergies. Some times as much as 150 to 200 mg. are given, and then reduced to 25 mg. every day or every second day. Favorable results have been obtained by the use of these hormones for allergic skin diseases such as atopic and disseminated dermatitis. Drug eruptions are helped; pruritus vulvae and pruritus ani respond well to the use; urticaria, angio-neurotic edema, and exfoliative dermatitis have all shown improvement by its use.

The so-called "diffuse collagen diseases" such as dermatomyositis, periarteritis nodosa, lupus erythematosus disseminatus, and scleroderma, improved under their use. Periarteritis nodosa is particularly benefited, but only temporarily. Acne due to iodides and bromides, as well as fixed eruptions, have also been helped.

Sulzberger has pointed out that these hormones are good anesthetics, as well as good analgesics, and he has found that no beneficial effects of topical application of the hormones have been observed in any strength. He speculates it is a mystery that they do no good even in open lesions, or have no effect when injected under the lesions. He indicates that this may be a fundamental factor in understanding the effect of these hormones.

Oral administration of Cortisone is quite as satisfactory as when administered intramuscularly, and has the same results. Cortisone should never be given intravenously. When beginning Cortisone, the patient should be given a sufficiently large dose to bring the disease under control as quickly as possible. When the desired degree of remission has been attained, an attempt should be made to reach a maintenance level by reducing the daily doses by 10-15 mg. every two to three days, compatible with satisfactory clinical progress.

There are two schools of thought concerning the administration of Cortisone. Some prefer "courses" at different intervals; others employ daily maintenance doses for prolonged periods. The oral tablets (Cortisone Acetate) are readily absorbed in most instances. It is of relatively

shorter duration than when injected, and it is necessary to administer this form in divided doses 2-4 times daily. Daily maintenance doses for prolonged periods are more generally used since this procedure has given very good results with only a minimum of untoward reactions. Both Cortisone and ACTH affect only the reversible tissue reactions; not the irreversible residues of susceptible disease.

The use of combined antibiotics when indicated is advisable particularly where there is the possibility of concurrent infection. I have seen cases of status asthmaticus show dramatic improvement in 3-4 days, taking only 25 mg. three times a day. However, a too low dosage of Cortisone may result in failure.

The contra-indications for the use of ACTH and Cortisone are the presence of a marked hypertension, nephritis, cardiac lesions or low cardiac reserve action, moderate but arrested tuberculosis, diabetes, peptic ulcer, furunculosis, or clinical endocrine imbalance. These hormones can be used with caution in patients with heart disease and with moderate hypertension; and in diabetes, providing there is use of diabetic control with insulin or diet.

Occasionally one hears indirectly of a patient who has had one course of treatment with ACTH or Cortisone and has gone many months without further treatment. This is erroneous, as cessation of ACTH or Cortisone therapy has always been followed by relapse to the original condition. Patients with asthma would go the longest without, but this was rarely over a month's duration. If patients do not respond to these hormones on the first course given in the doses herein recommended, there is little or no benefit on subsequent courses. Their greatest use is in the self-limiting allergic conditions and the treatment of status asthmaticus. They do not take the place of a careful diagnostic survey, elimination measures, immunization, and medical or psychotherapy. If given in the doses and method described, it can be given for some time in the older infectious or combined infectious and allergic asthmatic group of patients. Those patients obviously with limiting conditions may remain in remission.

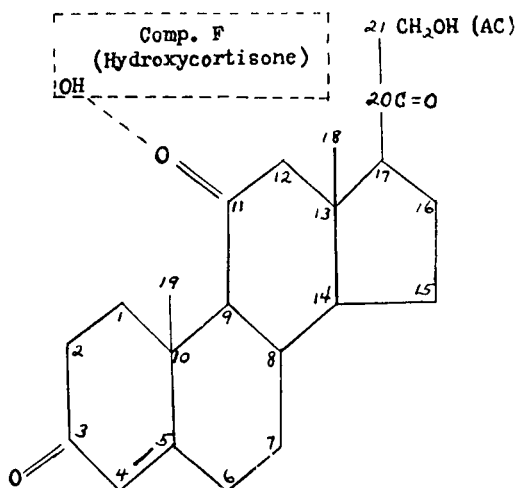
In some who have previously had remissions, treatment with these hormones may initiate a long symptom-free period, especially if the causative allergens and elimination and *immunization therapy* with the inhalant allergens is continued. Older chronic asthmatic patients with continuous wheezing remissions are short-lasting, but they may be maintained on doses of 6-10 mg. at intervals no greater than forty-eight to fifty-six hours.

Let us hope that with the purification of these hormones and the possible development of other important steroids, this form of hormonal therapy may be safer and more universally used. With accumulated experience the determination of optimal methods of using these potent hormones may be anticipated.

RESUME

CH Oxysteroids Cortisone (Compound E) and related steroids.

SUPPLEMENTARY OUTLINE

*Adrenal Cortex Influence.*

Metabolic Effect.

Increases:

Protein metabolism	
Fat metabolism	
K	} Secretion
Ph	
Urate	
CH (blood)	

Decreases:

Growth
CH Tolerance
Insulin secretion
Sodium excretion
17-ketosteroids

Inflammatory phenomenon will appear in the same location (always locally).

Injection of aqueous adrenalin cortex extract increases basal metabolism and muscular tone before sugar appears.

Adrenalectomized animals go into extreme weakness, muscles are

Injection of aqueous adrenal cortex extract increases blood pressure and muscular tone before sugar appears.

affected, and they go into shock and die. This is not due to muscle or nerve stimulus, but to early fatigue caused by fall in blood pressure (always precedes the fatigue).

When noradrenalin is injected, there is a temporary rise in blood pressure, and muscular contraction. Signs of stress are not due to removal of the adrenal cortex but are due to a metabolic disturbance—a failure of the peripheral vessels (not cardiac)—a *peripheral vascular failure*.

Adrenalectomized animals show a definite less and less response to adrenalin and die, but *adrenal cortex* extract injection evokes an adrenalin response and continued supply, and the adrenalectomized animal becomes normal.

Dog Experiments: Repeated injections of adrenalin—death.

„ „ „ cortical extract—normal.

Cortisone itself has no effect on vasoconstriction.

Speculation: Excites anterior pituitary gland with liberation of ACTH and stimulation of adrenal cortex.

Stimulation of vast network of all blood vessels (receptors) supplying the *autonomic system*. There is a good effect of cortisone directly in the area of small blood vessels, but not a major effect of the network of arterioles as such.

Similar reaction of inability of the autonomic nervous system is obtained by giving banthine. This working hypothesis, if used properly, shows a way of approach.

Cortisone, applied locally to normal, traumatized or hypersensitive tissues, produces local effects.

Sex hormones on the skin produce a systemic reaction. Affects the collagenous fibers (fibroblasts and ground substance).

Hyaluronidase produces an enzyme spreading action. The anti-hyaluronidase effect of 17-hydroxy-11-dehydrocortisone is definitely known.

CARDIO-VASCULAR ALLERGY¹

By

JOSEPH HARKAVY, M.D.

Involvement of the cardio-vascular system in man as a result of sensitization to foreign proteins indicates that the heart and blood vessels may act as a shock tissue similar to other forms of hypersensitiveness. The basis for our understanding of cardio-vascular allergy is to be found in the experimental observations made in systemic and local anaphylaxis.

Blod vessels. Evidence of the role of blood vessels in anaphylaxis has been obtained in the microscopic visualization of the ear lobe of serum sensitized rabbits and mice following reinjection of serum. In the sensitized rabbit vascular participation is characterized by arteriolar contraction, migration of leucocytes through the walls of capillaries and venules. In the sensitized mouse it is manifested by the simultaneous constriction of arteries and veins which is not influenced by blood pressure in the larger vessels or nerves. It may also appear in the absence of any outward manifestations of shock. This indicates that the vascular reaction is of local origin and is the result of the antigen and antibody interaction. (McMaster and Kruse, *J. Exper. Med.*, 89, 583, 1949).

Capillaries. Active participation of the capillaries is best noted in local anaphylaxis. In the frog's mesentary the acute local reaction is characterized according to Froelich and Roessle, by capillary stasis with engorgement by plasma, diapedesis of leucocytes with edema of the contiguous nerves. In the lungs of the egg sensitized rabbit following intranasal installation of purified egg albumin, there is at first increased capillary permeability and later severe vascular injury the extent of which depends upon varying intensities of antigen-antibody union. Thus there is edema, alveolitis, pneumonic consolidation and scattered areas of arteritis and phlebitis.

The delayed local anaphylactic reaction or Arthus phenomenon in the rabbit is characterized by severe necrosis. It is distinguished histologically by an inflammatory reaction in the connective vascular tissue both in the experimental animal and man. This reaction consists of fibrinoid degeneration of the ground substance, i.e. collagen in the

¹ Read before the second meeting of the "Spanish Society of Allergy".

connective tissue and blood vessels with formation of granulation tissue surrounded by histiocytes and fibroblasts. These changes may be elicited in the myocardium, heart valves, arteries, veins, lymphatics, lymph glands in many other shock organs. The reaction affects mainly tissues of mesenchymal origin. It manifests itself in marked edema, hemorrhages, leucocytic infiltration of walls of blood vessels, swelling and degeneration of endothelium, thrombosis and necrosis followed by scar formation.

Heart. Demonstration of specific reactions in the heart of the sensitized animal in the absence of any nervous influences gives support to the concept that the myocardium as such, may act as a shock organ. Evidence to this effect has been furnished by Witebsky and Szepeswohl. (*Compt. rend. Soc. de biol.*, 115, 1019, 1934). These investigators have shown that the vascular network of a three day old chick embryo which contains Forsman's antigen goes into shock following the application of Forsman's antisera. This is characterized by the shrinking of the embryo which sinks into the yolk followed by a total standstill of the heart. Similar phenomena were demonstrated by Wittich during anaphylactic shock in 18 day old chick embryos.

In addition to effects on the primitive heart, specific reactions in the coronary arteries of guinea pigs sensitized with horse serum following exposure to small amounts of homologous antigen have been shown to be present by Willcox and Andrus. These reactions recorded electrocardiographically by direct leads applied to the isolated heart are characterized by acceleration of the heart rate, alterations in the amplitude of contraction, prolonged P-R interval and deviations in the RS and T complexes. Abnormal electrocardiographic patterns consisting of bradycardia, tachycardia, ventricular extrasystoles, auricular fibrillation and periods of bundle branch block have also been demonstrated by Mikulicich, (*Journ. Allergy*, May, 1951) in the sensitized rabbit that had received a second injection of specific antigen, eggwhite or horse serum, 14 to 17 days after the primary injection. The majority of rabbits manifested these abnormal cardiac changes with small doses of specific antigen, without any evidence of general systemic reaction except for occasional cyanosis.

Vascular Localization of the Antigen-Antibody Reaction.

Tracer studies with labeled antigen to localize the site of its concentration during anaphylactic shock in guinea pigs by Warren and Dixon, (*Amer. J. Med. Sc.*, 216, 136, 1948) indicate that the labeled antigen, horse serum, albumin and globulin, concentrates in the edem-

atous collagenous tissue of the bronchial walls of the adventitia of pulmonary vessels. They concluded that the antigen-antibody reaction was related to edema formation. This would suggest active participation of blood vessels. However, the authors felt that the method used by them was insufficiently refined to localize radioactive material in individual cells fibres. Presseman (Journ. Allergy, Sept, 1951) studied this problem by using antisera prepared against rat kidney which he injected into rats for the purpose of localizing antitissue antibodies labelled with radio active substances (iodine tracer 131). Radiographs of the iodinated globulin fraction of the anti rat kidney serum employed in the injection, indicated that the former was localized in the glomerular tuft rather than the tubules. This was also substantiated microscopically. Pressman concluded from his experiments that the vascular bed, i.e. vessels of the kidney, was the seat of localization of antigen-antibody reaction.

Perfusion studies of vascular systems of organs removed from guinea pigs previously sensitized with horse erythrocytes with thoroughly washed horse's blood cells, led Nolf and Adant to conclude that the anaphylactic response of these organs was due to release of histamine by the vascular endothelium, as a result of the reaction between the latter and the injected antigen.

Since there is no experimental or histologic proof that the smooth muscle is the primary site of the antigen-antibody reaction in man, the probability is that in human hypersensitiveness the primary point of contact between the specific antigen and antibody is the vascular endothelium and the tissues immediately adjacent to it.

In the light of the above experimental data the clinical aspects of cardiovascular allergy gain increasing support. Our investigation of this subject begun in 1932 may be divided into two parts. The first deals with a) the factors concerned in the development of the cardiovascular system as a shock organ in man; b) the common non living allergens responsible for sensitization and c) the clinical manifestations resulting therefrom. The second part is concerned with cardio-vascular manifestations due to sensitization by bacterial agents and antibiotics.

/ PART I.

A. *Factors in the Development of Cardio-Vascular Shock Organ.*

- 1) Heredity.
- 2) Non-specific factors, infections, bacterial toxins, trauma, chemical and physical.

B. *Exciting Agents.*

Inhalants, tobacco, food, drugs, chemicals, foreign sera, antibiotics and bacteria.

C. *Elements of the Vascular System Involved and Clinical Manifestations.*

- 1) Capillaries-urticaria, angio-edema, purpura, local hemorrhagic necrosis. (Shwartzman phenomenon). (Etiology, food, drugs, bacteria).
- 2) Peripheral vessels—a) Migrating phlebitis. b) Thrombo-angiitis obliterans. (Etiology, tobacco, food, infection).
- 3) Heart-Arrhythmias such as extrasystoles, simple paroxysmal tachycardia, auricular fibrillation, angina pectoris, coronary artery disease. (tobacco, food, drugs, such as salicylates, pollen, immune sera, typhoid vaccine, infection, physical agents, cold and heat). Of these the most common is tobacco allergy. This was discussed from the experimental and clinical points of view. Treatment consists of avoidance of the offending substance.

PART 2.

Cardio-Vascular Manifestation due to Bacterial Allergy and Antibiotics.

The second part is concerned with a study of 21 patients who presented histories of respiratory allergy characterized by vaso-motor rhinitis, chronic sinusitis, cough and bronchial asthma. In 18 of these cases upper respiratory infections were followed by exacerbation of severe asthmatic seizures associated with fever ranging to 104°F., migratory pulmonary infiltrations with eosinophilia between 10 to 60 per cent and WBC varying from 7000 to 50,000. Concurrently with these symptoms there appeared 1) electrocardiographic abnormalities indicative of myocardial involvement, 2) reactions in the serous membranes, characterized by eosinophilic effusions in the pleura, pericardium and peritoneum, 3) involvement of the abdominal viscera including the liver, spleen, gastro-intestinal tract, 4) skin lesions characterized by urticaria, purpura, angio-neurotic edema, etc.

Study of the possible exciting factors responsible for these clinical

symptoms led to the opinion that bacterial infection originating in the infected sinuses and lungs were of major significance. In 13 of the 18 cases sensitization to pollens, inhalants and foods as revealed by positive skin reactions was found to play a synergetic role in the precipitation of some of the asthmatic episodes. The nature of the bacterial infection in the lungs was investigated in detail in six of the cases by means of the bronchoscope. The latter revealed marked pallor and edema of the bronchi. Smears of the secretions showed numerous eosinophile cells. Pure strains of pneumococcus 5, 6 and 11 were cultured from the material removed from the bronchi via the bronchoscope. Studies of the sputa showed a mixed flora of pneumococci, staphylococcus hemolyticus, streptococcus viridans, etc. The sinus washings showed similar organisms. Four of the six patients whose bronchial secretions contained pneumococcus 5, 6 and 11 showed positive skin reactions to the stock polysaccharide fractions of these organisms, as well as corresponding serum agglutinins and precipitins. The positive skin reactions consisted of the immediate urticarial as well as of the delayed tuberculin type. The delayed reactions were associated with generalized urticaria in two of these patients and acute asthmatic attacks in two others. Intracutaneous tests with autogenous vaccine containing staphylococcus A, non hemolytic streptococci and micrococcus catarrhalis recovered from sinus washings were followed in a fifth patient by a severe anaphylactic shock and asthmatic paroxysm, and in the sixth by a recurrence of pulmonary infiltrations, fever, cough, generalized petechiae and echymosis in the calf of one leg. These reactions as well as the urticaria were regarded as manifestations of bacterial allergy. Although no detailed bacteriologic studies were carried out in the other twelve of the eighteen cases, it was believed, in view of the close similarities in the histories of chronic respiratory infections leading to the development of clinical syndromes identical in most respects with those manifested by the above described six cases, that bacterial allergy also played a dominant role in the other cases of this group.

Penicillin and sulphadiazine sensitization, were considered to be responsible for the clinical manifestations in the remaining three of the twenty one cases. In the first two of these patients, symptoms fever, asthma, pulmonary infiltrations with eosinophilia, electrocardiographic abnormalities, etc. appeared ten to fourteen days after the administration of penicillin. These symptoms resembled a serum sickness type of reaction. The third case developed pruritus and generalized malaise with progressive enlargement of the liver and spleen and eosinophilia,

which followed the administration of sulphadiazine. In this patient a pure culture of a Taylor pneumococcus was also obtained from the infected right antrum, three years after the onset of his illness. The duration of this infection could not be determined.

Clinical Course and Treatment. Eight of the twenty one cases recovered completely under symptomatic therapy. This included treatment of infected sinuses surgically and with antibiotics, etc. In these cases the pulmonary, cardiac and serous membrane lesions were reversible. Eleven died, one developed chronic cardiac insufficiency while another disappeared from observation.

Four cases were treated with ACTH and cortisone. Of these a seventeen year old young woman, greatly benefitted from the cortisone therapy. In this patient the hyperergic reactions were limited to the lungs and heart. The pulmonary lesions consisting of eosinophilic infiltrations which had prevailed for eighteen months completely disappeared after two courses of cortisone treatment. The irreversible myocardial damage however, characterized by right bundle branch block remained unchanged. Although this patient has had recurrences of pulmonary infiltrations for two years she still gets occasional asthmatic attacks which are readily controlled with cortisone. The other three cases died because irreversible changes in various organs despite the fact that hormonal therapy was begun early in the disease.

Six of the twenty-one cases came to autopsy. In a seventh, biopsies of the enlarged liver and spleen were obtained six months prior to exitus. The general necropsy findings consisted of hyperergic vascular disease with granulomatous changes in various organs. This was conspicuously present in the lungs which manifested pulmonary infiltrations during life. Here the vascular lesions varied from simple thickening of small arteries to acute arteritis as well as necrotizing arteritis and endarteritis. In one case there was thrombosis of small arteries and veins associated with areas of hemorrhagic infarction of the lung.

The lesions in the heart were as follows: Case one manifested a diffuse inflammatory reaction of the myocardium consisting of an eosinophilic exudate superimposed upon chronic granulation tissue. In case two, the coronary vessels showed typical lesions of periarteritis nodosa. In case three myofibrosis with diffuse infiltration of the myocardium with eosinophiles was the outstanding feature. Case four showed diffuse fibrosis of the myocardium as well as periarteriolar fibrosis. The heart which was the only organ affected in case five, disclosed diffuse eosinophilic infiltration with granulomatous nodules. In the sixth case which

was due to penicillin sensitization, the myocardium showed diffuse fibrosis with very little change in the coronary vessels. Additional features in this case were allergic granulomatosis of the aorta associated with generalized necrotizing arteritis and focal fibrosis.

The gastro-intestinal tract was involved in four cases. Two showed obliterative endarteritis and recannalized vessels in the infiltrated serosa. The third case revealed ulcerative colitis and obliterating endarteritis. The fourth patient whose symptoms were due to penicillin sensitization, showed ulcerations and erosions of the entire gastro-intestinal tract with acute gastric ulcers with passive bleeding. This patient had received ACTH and cortisone without any results. There was a question as to the relationship between ACTH therapy and the gastric ulcers.

The liver showed periarteritis nodosa and amyloid disease in two cases. In a third case granulomatous areas resembling tubercles was present. In a fourth case in which sulphadiazine was suspected as playing an etiological role a biopsy showed periportal infiltrations with eosinophiles. In a fifth case fibrosing arteritis prevailed. In a sixth case (penicillin sensitive) there was acute hepatic necrosis.

Kidneys. Only two of the six cases manifested renal involvement consisting of active and healed lesions of periarteritis nodosa. In one of these patients amyloidosis was also found.

Spleen. Granulomatous areas were observed in the spleen in one case. In a second the spleen belonging to the patient who had received sulphadiazine, weighed 1100 mg. Histologic studies revealed stenosing endophlebitis and focal obliterating arteritis as well as periarteriolar sclerofibrosis. In addition there was diffuse eosinophilic infiltrations of the splenic pulp, increase of the fibrillar reticulum together with multiple anemic infarcts.

The uterus in one case showed endoarteritis obliterans.

Lymph nodes. In two cases the excised lymph nodes revealed eosinophilic lymphodanitis with focal fibrosis.

IONTOPHORESIS PAR L'HISTAMINASE DANS LES AFFECTIONS ALLERGIQUES DE LA PEAU

(Résumé)

Par

Dr. MORETTI et Dr. MARTINEZ BULA

Montevideo

Le but de cette étude est de présenter un nouveau procédé pour le traitement des maladies allergiques de la peau, par l'histaminase, à l'aide de l'iontophoresis.

On commence par l'exposé des bases de l'iontophoresis, l'action des ions négatifs et positifs, la manière dont ces ions pénètrent dans la peau à travers les glandes sudoripares et le bulbe capillaire.

On y décrit aussi l'application de cette méthode, la concentration de l'histaminase (1 gr. dans 600 cm.³ d'eau distillée) mise à l'aide d'un milliamperage, entre 1/2 et 2, de 15' à 20 minutes par jour, ou tous les deux jours. La quantité de séances varie entre 8 et 10 applications.

Le nombre total des cas ainsi traités est présenté dans un tableau schématique et une analyse statistique finale démontre que l'effet de la méthode est réel et pratique.

Les photographies de certains des cas traités sont exposées dans un album.

A PROPOS DE QUELQUES CAS DE RHUMES DES FOINS

(Résumé)

Par

le Dr. R. ALEMANY-VALL

Barcelona

Dans les cas étudiés dernièrement nos malades étaient sensibles au pollen de Plantago, Platane, Graminées et Pariétaire officinalis. Chez tous ces patients il y avait éosinophilie nasale et une muqueuse plutôt pâle dans les cas de sensibilité au Platane et aux Graminées, et rouge et irrégulièrement hyperplasiée dans les cas de sensibilité ancienne et intense au pollen de Pariétaire officinalis.

Les réactions cutanées étaient positives aux extraits de pollen sensibilisant et en dehors des saisons polliniques ces malades avaient des rhumes de cerveau ordinaire très différents de leurs coryzas allergiques

durant la saison du pollen sensibilisant, le traitement spécifique agissant favorablement dans ces deux genres de coryzas.

A Barcelone la saison du pollen de Platane suit un cours très régulier commençant au milieu de mars pour se terminer trois ou quatre semaines après. La Pariétaire fleurit presque toute l'année et les symptômes s'en manifestent de Mars à Juillet, inclusivement. Et dans ces cas, le malade sait généralement quelle est la plante responsable de son état, car elle se trouve dans son ambiance immédiate. Les patients sensibles aux Graminées sont malades d'Avril à Mai ou de Mai à Juin. Ils ne connaissent pas la plante allergène et leurs symptômes se trouvent accrus durant un voyage par la quantité de pollen absorbée.

L'arome de certaines plantes : narcisses, glaïeuls, lis, etc. peuvent donner des troubles rhinorrhéiques et de la conjonctivite avec enflure de la paupière chez les malades sensibles aux Graminées et chez les rhinitiques anciens et invétérés.

En général, le rhume des foins commence par une rhinite suivie quelques années plus tard par un asthme associé. Nous avons vu un œdème de la glotte provoqué par le pollen de la Pariétaire.

Nous avons vu un cas de réaction constitutionnelle à l'injection de *Plantago*.

Le traitement spécifique fait disparaître l'asthme, mais la rhinite se montre plus rebelle dans les cas invétérés; il est de très bon résultat dans les cas de rhinite simple ou de conjonctivite pollinique. Les antihistaminiques sont d'effet transitoire.

TRAITEMENT DE L'ASTHME PAR LE PREGNANDIOL PROVENANT DU MEME ASTHMATIQUE

(Résumé)

Par

le Dr. R. ALEMANY-VALL

Nous avons utilisé comme traitement, chez les asthmatiques ayant de très évidentes crises prémenstruelles qui disparaissent pendant la grossesse dans la plupart des cas, le Pregnandiol extrait de l'urine de ces mêmes asthmatiques (procédé Astwod et Jones) par le chimiste Mr. Hernandez.

Le Pregnandiol fut donné sous forme de piqûres, et bien que la quantité injectée fut très petite, nous obtinrent de bons résultats thérapeutiques dans les douze cas suivis et étudiés durant deux ans.

Nous ignorons si le Pregnandiol agit spécifiquement (les cas étudiés n'étant pas d'origine endocrinienne) ou nonspécifiquement à la façon de l'histamine azoprotéique qui nous a donné parfois d'excellents résultats.

Nous imaginâmes ce procédé encroyant qu'il est souvent préférable de se servir des produits procédant de l'organisme du malade, prenant exemple sur l'injection de sérum ou d'urine utilisée spécialement dans les cas d'allergie dont nous ignorons la cause, car l'allergène peut se trouver dans le sérum sanguin et être éliminé dans l'urine.

Il est bien connu que le Pregnandiol se trouve très augmenté dans les urines des femmes enceintes.

CARACTERISTIQUES IMMUNO-ALLERGIQUES DE LA TUBERCULOSE DES Jumeaux

Par

G. ROMERO ESCACENA et J. LÓPEZ MEJIAS

Parmi les lésions tuberculeuses des jumeaux, on trouve une ressemblance plus étroite que celle généralement admise, comme en déduisent les auteurs de l'étude de deux couples de jumeaux, provenant les uns de grossesse bivitelline, les autres univitelline.

Il faut chercher la ressemblance non seulement dans l'ordre pathomorphologique (parce qu'à cet égard les multiples répercussions du milieu ont une grande influence), mais aussi dans la forme évolutive, dans le sens des réactions organiques, etc., et, en résumé, dans l'analogie des réponses immunoallergiques.

CORRELATION ENTRE CRISES ASTHMATQUES ET CHAMPIGNONS DANS L'ATMOSPHERE DE SEVILLE

Par

F. MOLINÉ DEL CASTILLO

Seville

L'étude suivante a été réalisée: on a contrôlé tous les malades qui ont consulté pendant une année, choisissant seulement ceux qui présentaient une sensibilité claire et évidente aux champignons, qualifiant leur état comme malades avec crise ou sans crise, établissant un index d'asthmatiques pour chaque mois en divisant le nombre de crises par

le nombre total de malades. Ces index furent comparés avec le nombre de colonies de champignons obtenu pendant ces mois-là, donnant un index de corrélation de morbidité asthmatique à un nombre de colonies égal à $+ 0,481$ avec un erreur probable de $0,146$, index assez remarquable parmi ceux qu'on a l'habitude d'obtenir dans les observations biologiques. — Le fait qu'il soit positif indique qu'à un plus grand nombre de colonies d'un mois, un plus grand nombre d'asthmatiques entrent en crises ce même mois. —

Quand on calcule graphiquement la ligne de corrélation on observe que sans l'existence de champignons dans l'atmosphère de Séville se présentent des attaques chez ces malades, d'où l'on deduit qu'on ne peut pas attribuer toutes les attaques aux champignons, mais qu'il y a encore d'autres facteurs qui y participent (météorologiques, allergènes, intrinsèques, etc.) et qui n'ont pas été évalués dans cette étude. —

En faisant le calcul de corrélation entre les malades sans attaques avec le nombre de colonies, on obtient un index de $- 0,562 \pm 0,196$, le signe négatif indique qu'à moins de champignons plus de malades sans attaques. —

La conclusion en est que l'augmentation du contenu mycogène atmosphérique augmente le nombre de crises chez les malades sensibilisés à eux et vice versa, et que ces attaques peuvent être provoquées aussi par d'autres facteurs différents aux champignons. —

*List of Communications Presented at the 2nd Spanish Congress
of Allergy. Sevilla, October 1951*

Accion de la Mostaza Nitrogenada sobre la formacion de anticuerpos:

Prof. Jimenez Diaz y Dr. Perianes. Madrid.

Ulteriores estudios sobre la histamina en heces: *Prof. Jimenez-Diaz y*

Dr. Arjona. Madrid.

Asma y mostaza nitrogenada: *Prof. Jimenez-Diaz y Dr. C. Lahoz.*
Madrid.

Reacciones cutaneas con fracciones bacterianas: *Prof. Jimenez-Diaz y*
Dr. Ortega. Madrid.

Interpretacion y resultados de las microprecipitinas: *Prof. Jimenez-Diaz*
y Dr. Segovia. Madrid.

La anatomia radiologica del asma; estudio con una nueva tecnica de
exploración: *Prof. Jimenez-Diaz y Dr. Lahoz Navarro.* Madrid.

El neumotacograma en el asma bronquial. — Nuevos aportes a la pato-
genia del ataque asmatico: *Dr. Lopez-Botet.* Valencia.

- Profilaxis de la alergia respiratoria a polvo: *Dr. Posse*. Bilbao.
 Tratamiento del asma con cortisona y ACTH: *Dr. F. W. Wittich*.
 Mineapolis.
 Iontoforesis en las enfermedades alergicas: *Dr. Moretti*. Montevideo.
 Ansiedad y asma: *Dr. Lopez Ruiz*.
 Caracteristicas alergico-inmunitarias de la tuberculosis en gemelos:
Dres. Romero Escacena y Lopez Mejias. Sevilla.
 Polinosis: *Dr. Alemany-Vall*. Barcelona.
 Pregnandiol en el asma: *Dr. Alemany-Vall*. Barcelona.
 Correlacion entre estados asmaticos y cantidad de hongos cultivados en
 las zonas colindantes con Sevilla: *Dr. Molini*. Sevilla.
 Primeros resultados en los tratamientos del asma bronquial por la
 mostaza nitrogenada: *Dr. Cruz Auñon*. Sevilla.
 La posibilidad de complicaciones organicas vasculares en el curso de las
 crisis de jaquecas inveteradas: *Dr. Roda*.
 Nueva contribucion al problema de la alergia constitucional: *Dr. Roda*.
 Un caso de monosensibilizacion polinica especifica: *Dres. Jimenez-Diaz,*
Lopez Barrantes y Cantó Borreguero. Madrid.
 Observaciones clinicas sobre las dermatitis alergicas y el eczema: *Dr.*
Giorko. Las Palmas.
 Accion de los antihistaminicos en las cardiopatias: *Dres. Lozano Lopez,*
Draeger y Carretero. Sevilla.
 Micosis pulmonares: *Dres. Alix y Dr. Canto*. Madrid.
 Alergia digestiva (dos comunicaciones): *Dr. Romero Rodriguez*.
 Sevilla.
 Lesiones vasculares de origen alergico: *Dr. Harkavy*. New York.
 Problemas diagnosticos en el asma bronquial: *Dr. Waldbott*. Detroit.

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