

ALLERGY, ANTIBIOTICS AND CHEMO- THERAPEUTICS

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BACTERIAL ALLERGY

According to our present knowledge, bacteria, virus (214, 266) and fungi have an undeniable influence, though of an obscure nature and undefined characteristics, on the genesis, intensity and duration of the allergic manifestations.

This conclusion is based on the following:

1. The frequency with which allergic symptoms start after an acute focal or general process, of a proved infectious nature, i.e., asthma following a series of bronchial infections; eczema following a streptococcal intertrigo, etc.
2. The cases where a constant sequence is established between the exacerbation of a chronic infectious process and an allergic manifestation, i.e., an acute varicose epidermo-dermatitis provokes the appearance of secondary reactions of an eczematous nature, etc.
3. The positive reactions of a tuberculous type (44, 93, 113, 319, 394)—and even immediate urticarial (61, 236, 440)—noticed in some allergic patients when their skin sen-

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- sitivity is explored with diverse bacterial species isolated from different septic centres (41, 426).
4. The disappearance or noticeable diminution of the allergic symptoms subsequent to the extirpation of a septic centre, or the adequate treatment of a concomitant infection, i.e., the disappearance of asthma following cholecystectomy or appendicectomy; of eczema through the correct treatment of pyodermitis; etc.
 5. The undoubted benefits that are usually obtained by correctly applied hyposensitizing vaccinothrapy (45, 245, 367, 375, 394).

SEPTIC CENTRES

The most commonly known septic centres are the following:

Bronchi: partial or total bronchitis, bronchiectasis.

Paranasal Sinuses: maxillary, frontal, ethmoidal and sphenoidal sinusitis.

Pharynx: tonsillitis, pharyngitis, adenoiditis.

Ear: otitis, mastoiditis.

Eyes: dacryocystitis.

Teeth: paradentosis, periodontitis, suppurated pulpitis, osteitis, periapical cyst or granuloma.

Stomach and Intestines: gastroenteritis, appendicitis, colitis, proctitis, intestinal dysbacteriosis.

Biliary Channels: cholangitis, cholecystitis, choledocitis.

Urinary Conducts: pyelitis, cystitis, urethritis.

Genitals: prostatitis, vesiculitis, oophoritis, salpingitis, endometritis, cervicitis, colpitis.

Skin: pyoderma, mycosis.

Bones and Articulations: osteomyelitis, infectious arthritis.

GERMS

All and every kind of germs may cause allergy, but the most frequently incriminated are the following:

<i>Respiratory Allergy</i>	{ Gram positive	{ staphylococcus albus streptococcus hemolyticus streptococcus viridans diplococcus pneumoniae
	{ Gram negative ac. resisting bact.	{ klebsiella pneumoniae neisseria catarrhalis mycobacterium tuberculosis escherichia coli hemophilus pertussis
<i>Cutaneous Allergy</i>	{ Gram positive	{ staphylococcus albus streptococcus
	{ Gram negative	{ pseudomonas aeruginosa
	{ Fungi	{ trichophyton microsporum candida epidermophyton

From a theoretical point of view it may be accepted that the action of the microbial elements result from one or several of the following mechanisms:

- a) the antigenic character of the microbial bodies or of their toxins (49, 285, 368) (direct antigenic action);
- b) the modifications of certain organic elements which transform them into autoantigens (indirect antigenic action);
- c) the liberation of bacterial metabolites which are able to act directly on the cells or enzymatic systems, thus setting free the allergic phenomena (effective action);
- d) the diminution of the level of tolerance of the organism—breakage of the allergic balance—thus permitting the exteriorization of a subliminal hypersensitivity so far latent, caused by other allergens (revealing action);
- e) the nonspecific action, which localizes, in certain shock-organ, an allergic syndrome which had appeared in other parts of the organism or at different levels of the same system (fixative action).

CHEMOTHERAPEUTICS AND ANTIBIOTICS IN ALLERGY

Admitting the germs' causal participation, it is natural that chemotherapeutics and antibiotics be used in an effect to counteract or annul the different means of action.

The prescription of these therapeutic agents is, of course, absolute, when there is a clinically active infectious process closely related to the symptoms.

In those cases where septic centres exist, even though they may not have a marked clinical symptomatology, it is also usual to attempt their sterilization through a general impregnation of the organism with antibiotics.

Finally, in some cases the therapy is undertaken as a last resource, when all other treatments have failed.

Whatever the special circumstances of the case to be treated may be, the general rules established by Fleming should be followed:

1. That they be used only in case of infections caused by germs that are sensitive to the antimicrobial agent.
2. That the germs and the antimicrobial agent come into contact with each other.
3. That a sufficiently high concentration be obtained at the focus to be sterilized.
4. That this concentration be maintained for a period of time sufficiently long to accomplish the desired effect.

A fifth rule should be added in our particular case: that the therapy be carried out with those agents and methods that offer greatest security against sensitization.

It is difficult to fulfill these conditions in the treatment of bacterial allergy. In fact, in the majority of the cases the identity of the causal germ can only be presumed, with a greater or lesser degree of certainty. The allergenic foci are frequently isolated from the general circulation and no asserive judgement exists which makes it possible to determine when a sufficiently high concentration has been reached, nor for how long the therapy should be continued.

This etiological uncertainty is partially solved by the use of those antibiotics which possess an extensive antimicrobial spectrum, but they present the drawback of being only, or above all, bacteriostatics, when an intense bactericide effect seems more desirable.

The difficulty of obtaining "in situ" an adequate concentration of the antimicrobial seemed obviated—in the case of respiratory foci—through the administration of aerosols, but this method presents the disadvantage that the foci are often inaccessible, either because they are located in the middle of the tissues, or because they are blocked out and isolated from ventilation (paranasal sinuses with impermeable ostia).

Even in those processes which appear to be most favourable, such as cutaneous allergies caused by microbes located in the skin, where the causal germ or germs may be isolated and thus make it possible to determine their sensitivity to the antimicrobial agents, and also obtain an effective local concentration of the latter, we sometimes come up against the disadvantage of the frequency with which sensitization is generated by the local application.

SULPHONAMIDES

The sulphonamides have caught the attention of specialists in allergy, due to the frequent manifestations of hypersensitivity which they provoke, rather than to the possibility of their application in allergic illnesses.

Notwithstanding, their administration by topical, oral and parenteral routes (13, 27, 59b, 286, 348, 359, 382, 423) has been used so that they may act on the several septic foci.

By this therapy, as it is logical to surmise, the infectious processes that occurred in allergic persons have benefited, without appreciably modifying the manifestations of hypersensitivity.

However, we must mention the employment of sulphonamides in nebulizations (9, 183, 282, 348, 373), a treatment which originated in our country (59) and which still continues

in use, because its effectiveness in the treatment of the respiratory foci is greater than that obtained by any other means of administration, since an accumulation of the drug in the infected organ is attained.

On the other hand, if, as it happens very frequently, the infected focus is totally or partially excluded, the concentration "in situ" obtained by this method and which only results from the systemic absorption of the medicament, is generally insufficient and has to be supplemented by oral or parenteral administration.

Its prophylactic use (133) in cases of allergic outbreaks subject to foreseen seasonal exacerbations and attributable to infectious processes, has allowed us to prove the lessening and more favourable course with the subsequent improvement of the resulting allergic state.

This treatment, the use of which has not been wide-spread, consists in the administration of a hypotonic sulphonamide for a period of several months, during autumn and winter. In our own experience, when applied with moderation, good judgement and in well selected cases, results similar to those mentioned by the originators of the method have been obtained.

In the latter period the sulpha-drugs, which had been practically superceded by antibiotics, have returned into favour, by virtue of the lesser toxicity of the most recent products, the discovery of the increased microbial resistance to antibiotics, the admitted advantages of the association of chemotherapies between themselves (240) and with antibiotics (33, 142, 148, 371), and their reduced cost.

SODIUM PARA-AMINOSALICYLATE

By means of sodium para-aminosalicylate administered in doses from 4 to 8 grs. daily during periods of one to two weeks, favourable results may be obtained in some rhinopathias and dermatosis, but they are nearly always temporary. Asthma does not appear to react so well to this medication (11a, 60, 235, 366, 410).

ISONICOTINIC ACID HYDRAZIDE

In our experience, and applied to bronchial asthma therapy, the above gave hopeful results, but requires ultimate confirmation. We employ doses varying from 200 to 300 mg., during two to four weeks.

PENICILLIN

The above is possibly the most employed agent (8), not only in the therapy of respiratory allergies¹, but also in cutaneous treatments².

The methods of administration and the doses are those commonly used in other treatments, with adequate modifications due to the special conditions of the allergic manifestations.

The frequency with which the above mentioned appear in the respiratory organs has given rise to the great use of aerosols in solutions (2, 16, 88, 102, 128, 141, 165, 172, 175, 199, 200, 262, 307, 331, 369, 407) or microcrystals (350, 351) of this antibiotic, which, given by the method described, presents the advantage of its very slight irritating action (113).

With the same purpose, although with different objects, we have recurred to the parenteral administration of various penicillin esters (leocilin (207) and estopen) which reach a very high concentration in the bronchial mucosa level and which, according to our experience, give slightly superior benefits to those obtained with the ordinary penicillins.

Also, in the cases of chronic asthma or status-asthmaticus the use of penicillin in higher doses and by the parenteral methods, has given good results, although of a temporary nature (22, 145, 242, 374).

At present we are statistically recording the results obtained with the application in doses of much higher quantities

¹ 2, 15, 16, 22, 472, 90, 127, 166, 174, 199, 200, 217, 242, 275, 307, 309, 311, 331, 341, 349, 350, 351, 369, 374, 387, 388, 396, 407, 409.

² 56, 57, 66, 156, 157, 188, 268, 405, 436.

than those administered hitherto and in association with other antibiotics.

In the same manner as with the sulphonamides the prophylactic use of penicillin has been experimented with by means of prolonged administration by the mouth (171), but this procedure, considered efficient by its originator, has not reached wide use, as far as we have been able to determine. Meanwhile, and also with encouraging results, other authors (127, 307) have administered it by aerosols.

Finally: The computation and consideration of reports referring to the use of penicillin, together with our own experience, based on the observation of more than 16,000 patients attending the Instituto Nacional de Enfermedades Alérgicas, allow us to affirm that with this antibiotic improvements between 25 % to 30 % are obtained in patients suffering from respiratory allergies, with bacterial components.

Aerosols appear to be somewhat more effective than the parenteral treatment by means of injections, at least with the relatively small doses with which this has been effected to date.

The therapeutic benefits are only temporary in the great majority of cases; which obliges us to repeat the treatment with the consequent risk of bringing about a sensitization, and to employ, as a supplement, different auto-vaccines or stock-vaccines which prolong the asymptomatic periods and avoid relapses, within certain limits.

In dermatology the parenteral use of penicillin in convenient doses has given excellent results in selected cases (57, 285), and is sometimes supplemented to advantage with local nebulizations (188, 285).

The topical application of ointments and creams is effective in cases of pure microbial eczemas—strepto and staphylococcal—it being advisable to use the antibiotic during a period of not more than 4 or 5 days, due to its high sensitizing capacity (66, 157, 268, 401, 456).

STREPTOMYCIN

The use of streptomycin is reduced to those cases due to streptomycin-sensitive respiratory or intestinal germs (159) and to its association with penicillin when it is desired to increase the power of the bactericidal effect of the latter (88). The specific action on the tuberculous bacillus is also convenient when concomitant phymic processes exist. It is used in injections or aerosols (88, 309) in doses of 0.50 to 1 g. daily, during more or less prolonged periods, in general, from one to two weeks.

The dihydrostreptomycin is used in a similar manner and appears to be slightly less sensitizing.

CHLOROMYCETIN, AUREOMYCIN AND
TERRAMYCIN

The use of these antibiotics, more recently known than the previous ones, is still in an experimental clinical stage (75, 324 b).

They present the advantage of a wide antimicrobial spectrum, speed of their bacteriostatic effects, very slight toxicity and the facility of administering them.

With these we have sometimes obtained good results in bacterial eczemas and asthmatic bronchitis which do not react to other antibiotics.

Some of the success obtained may be attributed to the sterilization of intestinal parasites, due to their amoebicidal action (292).

Others may be determined—and in this instance one must not set aside this factor in the correct evaluation of the efficiency of these antibiotics—to the emotional and suggestive phenomena which always accompany the administration of a drug which reaches us with the prestige of novelty, if not of “magic”.

In addition to the classical methods of administration, they may be used in aerosols (309) which are generally toler-

ated satisfactorily. For this purpose we wish to point out that aureomycin must be combined with etilendiamine to counteract its acidity.

Ointments are advisable in the therapy of dermatosis associated with pyogenic infections, due to its comparatively weak allergenic capacity (143, 358), although for some authors they have the disadvantage of losing their effectiveness on prolonging the treatment (143).

TIROTRICIN

It is used in topical applications; by aerosols, associated to vasoconstrictors (87), or in solutions and ointments, usually combined with penicillin (405).

It is an effective antibiotic, but of limited use due to the impossibility of its parenteral application.

POLIMIXIN AND BACITRACIN

They are applied, either separately or combined, in the form of 10 % ointments in the therapy of the manifestations of infected cutaneous allergies.

They are considered the least allergenic of the antibiotics when used by this route (131, 143, 274, 365).

They are also used as aerosols of bacitracin in doses of 25,000 to 50,000 units, alone or combined with penicillin. It must be borne in mind that this method only has a local topical action (308).

NEOMYCIN

Its local application with ointments is advisable in the treatment of pyogenic dermatosis (223), since it is only slightly sensitizing.

In conclusion, the results obtained with antibiotics are contradictory and have given rise to the publication of discrepant

statistical data and opinions, for which reason the use of these drugs is still in its early stages and subject to attention.

So much so, that the employment in allergy of these anti-microbial preparations has been, in our opinion, excessively empirical and has lacked a definite structural conception, which is a result, in its turn, of the weakness of our physio-pathogenic knowledge.

In spite of this uncertainty, we may affirm that therapy with chemotherapies and antibiotics may have two different objectives, of very different nature and effects, in spite of which they are sometimes confused:

1. The control of an infection in an allergic individual, which apparently only requires the diminution below a certain level of the number of germs.
2. The total cure, or the transformation of a bacterial allergy into a sub-clinical case, which would imply—in accordance with the theory and observations made in certain chronic infectious processes, such as tuberculosis and syphilis—the total or practically total destruction of the allergenic germs.

The analysis of the various publications issued, allow us to appreciate that a great part, if not the majority of the investigators, have tried to obtain this end result by means of doses and methods of administration of antimicrobial agents which have proved to be useful to obtain the first of the aforesaid objectives, of more restricted extent.

It seems reasonable to suppose, therefore, that the number of failures has superseded the number of successful cases, and this demands a readjustment of the therapeutical schemata with the object of making the utmost use of the possibilities of these agents by means of an adequate selection, dosing, administration and, above all, correct combination thereof, taking advantages of those which have their maximum power when acting conjunctly (208, 414) and rejecting those that inhibit each other (205, 371).

Moreover, even though it were possible to carry out a complete and definite suppression of the etiological microbial agent, the allergic manifestations might continue if the agent had acted only as a trigger, either by means of transformation of certain organic elements in autoantigens, thus starting a process which afterwards tends to continue spontaneously; or by the already known facilitation and subsequent fixation of the reflexes.

ALLERGY TO CHEMOTHERAPEUTICS AND ANTIBIOTICS

Above all, we must distinguish between intolerance to drugs and allergy to drugs.

Intolerance is that condition by which a small quantity of the drug produces symptoms which usually only appear in those who have received an excessive quantity of said drug: i.e., the instillation of a drop of atropine in the conjunctival sac produces face blush, extreme tachycardia, delirium, hallucinations, etc. These symptoms may be provoked in all persons by means of the administration of a sufficient dose.

On the other hand, in allergy to drugs, any quantity of these bring about, in hypersensitive individuals, the appearance of the symptoms belonging to allergic illnesses: urticaria, edema, rhinopathy, asthma, etc., whatever may be the allergenic drug.

PATHOGENY

The pathogeny of allergy to chemotherapics and antibiotics only constitutes a particular instance of what is generally accepted regarding cases of allergy to drugs (10, 52, 185, 233, 291, 325, 345, 383). It is admitted, in accordance with the theory set forth by Wolff-Eisner and developed by Lansteiner, that these compounds, lacking protein nature and, therefore, without any antigenic capacity of their own, act as haptens or incomplete antigens.

These would form compounds (68, 85, 178, 239) with the tissue or hematic proteins bringing about sensitivity, which afterwards could be released by the isolated hapten.

This hypothesis has received some confirmation with reference to penicillin, but, on the other hand, appears controverted by experiences carried out with sulphonamides (421, 422) and other drugs, which would suggest that the cutaneous sensitivity, at least, obeys different mechanisms (120, 122, 126, 355).

In accordance with the classical conceptions, allergy to drugs require, in order to develop its existence, at least two contacts with the allergenic agent: one, sensitizing, and, the other, precipitating. In apparent contradiction, there are certain cases in which the hypersensitivity is made known from the first recognizable contact with the drug.

These manifestations have been explained by the existence of a special and congenital idiosyncrasy.

Notwithstanding, we must not set aside the possibility of a previous unapparent contact, together with a placental transmission (206) of the specific antibodies. In certain occasions, these reactions also are a result of the existence of a previous sensitivity to other products related by their chemical structure to the release of chemotherapeutic or antibiotic agents. Thus, for example, the sensitivity to several preparations which have in their formula a benzoic nucleus with a radical substituted in the "para" position, may bring about a manifestation or a symptom from the moment of the first contact with a sulphonamide (12, 315, 401).

In the special case of penicillin, the sensitivity may be due to the inhalation of fungi and spores belonging to the penicillium gender (72), or to its ingestion (159), especially with certain varieties of cheese (roquefort or gorgonzola), or contaminated food.

The existence of a previos dermatomycosis caused by trichophytos which might have common antigens with penicillin, also seems to be important (384).

There are persons who even affirm that the possibility

exists of an intestinal contamination of a saprophytic nature by part of the penicillium (335), but this fact has not been confirmed.

Finally, certain allergic reactions consecutive to the first contact with chemotherapeutics and antibiotics, have been explained by the persistence of the drug in the organism, which would allow it to act successively as a sensitizing and a precipitating agent.

Various physiological conditions, in which a certain degree of neuroendocrine unbalance exists, act as allergy predisposing factors, as for example: puberty, menstrual periods, pregnancy and menopause. Several gastrointestinal and hepatorenal pathologic processes; the intercurrent infections; hypovitaminosis, calcium deficiency; inbalance of the blood electrolytes; etc., act in this same way.

A unfavourable influence is also exerted by abrupt climatic changes, certain seasons of the year, excessive exposure to light, and other cosmic or telluric factors which have not yet been elucidated.

ALLERGY TO SULPHONAMIDES

The wide-spread knowledge of therapy with these drugs brought about the increase in the appearance of toxic reactions and of hypersensitivity (43).

The sulphonamides of highest allergic power are: sulphathiazol, sulphapiridine and sulphonamide (249); the best tolerated are: sulphomerazine, sulphametazine and their isomer, elkodin, irgafen and gantrisin (261).

Sulphaguanidin, sulphasuccidin, phtalilthiazol and formocibazol (161, 184), used as intestinal bacteriostatics, are only slightly allergenic due to their reduced absorption.

In the majority of the cases the sensitivity (43) is specific to the causal drug and the reactions are provoked only by this, but, eventually, sensitivity to several or to all of the sulphonamides may exist (293, 422).

Also, sensitivity has been noted extending to all the preparations with the benzoic ring combined with a radical substituted in the position "para": local anaesthetics, analgesics, colouring agents, etc. (12, 315, 401).

Sensitization seems to depend on the prolongation of the time of administration, more than on the dose administered (109), although this fact has been discussed by some investigators (221).

With the exception of rare cases (167), the majority of the investigators agree that the interrupted treatment favours the appearance of allergic manifestations (302).

Sulphonamides may sensitize whatever their methods of ingestion or contact with the organism, but it is generally admitted that their local application is the most frequent cause of allergic reactions (14, 48, 132, 391).

When cholesterol and lanoline are used as excipients, they appear to favour sensitivity (104), and this is more frequent in certain conjunctival mucous zones or cutaneous regions (eyelids, flexural surfaces of the principal joints). Furthermore, the existence of a bacterial hypersensitivity, as occurring in chronic cutaneous infections, exercise a similar favourable effect (161).

Allergic symptoms may be released when administering the sulphonamide by a different route than that which brought about the sensitivity; i.e. sensitization by local topical application and precipitation by ingestion or vice-versa (247, 302).

In the first of these instances, the symptoms usually reside exclusively, or are more intense, at the point in which the sensitization was carried out. The possibility of an allergic reaction is greater when the sensitivity is due to local application and its precipitation by the same method, in order to diminish in the cases of oral precipitation and oral sensitivity (302).

Generally, sensitivity requires a certain period of time in which to develop. For this reason, it is more frequent one or two weeks after the administration of the drug, and less pro-

bable before four days have elapsed, although there have been responses two days later or after one single dose of two grams of sulphadiazine (238).

PATHOLOGY

The cases where it has been possible to carry out a post-mortem examination are very few. When this has been done we were able to observe the existence of lesions similar to those found in the anaphylactic shock following protein sensitization.

There is a predominance of fibrinoid necrosis of the middle tunic of the small and medium caliber arteries and exudates of monocytoïd cells with multiple parenchymatous lesions. On the whole, there is a gross hyperplasia of the reticulo-endothelial system and the capillary sinusoids appear to be crammed with macrophages which have phagocytosed red and white cells (38, 322).

SYMPTOMS

The most common reactions are cutaneous and of the mucosae, and may be general (209) or local.

In the general group there are:

Cutaneous Erythema: Morbilliform (1, 24, 97, 158, 334, 390, 424), scarlatinaform, psoriasiform (304), etc.

Urticaria (13) and *Angioneurotic edema*.

Vesicular Dermatitis: Eczema, contact dermatitis.

Phlyctenular, ampullar (168), *pemphigoid* (215) and *exfoliative dermatosis*.

Erythema multiforme (86, 391) and *nodosum* (169).

Purpuric Dermatitis.

Those of a local nature may be circumscribed to the places of application of the drug (instillation, ointments); they may occur in the places exposed to light—photosensitive action (39, 294, 300, 391)—or be limited to usually small regions, always the same, in those determined as fixed erythema (69, 95, 137, 270).

In some cases the cutaneous reactions reproduce symptoms of a pre-existing dermatosis, i.e. isomorphic reaction in psoriasis patients (197).

They may also produce lesions at the level of the phanerae: transitory alopecia or onychopathias.

The mucous manifestations usually consist in conjunctivopathies or rhinopathies (13).

Less frequently we find certain manifestations resulting from hemocytopoietic inhibitions. In some cases the erythrocytic section is affected and anaemias are generated; in other instances it is confined to the leukocyte section and is made manifest by agranulocytosis. There are cases where the thrombocytopoietic activity is inhibited, with consecutive thrombocytopenic (96, 229, 272) purpura. Finally, there are others of total aplastic anaemia (248, 380).

Also, rhinopathy and asthma (316, 468) attributable to these medicaments are rare.

Some authors (38, 125, 301) consider that certain renal manifestations characterized by anuria or oliguria, showing albumin, cylinders, red cells and cellular elements in the urine, and which may not be attributable to a tubular obstruction due to the precipitation of the drug, result from an interstitial allergic edema with intracapsular renal constriction.

Other reactions which also may be observed, can be included in the serum-sickness syndrome: fever, arthalgias, myalgias, polyadenopathies, hepatosplenomegalia, etc.

Finally, we may point out that Rich (320, 321) considers that certain cases of periarthritis nodosa (62, 246) and disseminated lupus erythematosus (151), appear as a result of allergy to sulphonamides.

ALLERGY TO PENICILLIN

The frequency and intensity of reactions to penicillin have suffered fluctuations in accordance with the changes experimented by the drug, since its first appearance, up to date.

Although the first amorphous penicillins did not show

toxic properties (140) when first used, they soon brought about reactions, particularly of a pyretic nature, but also allergic, attributable mainly to impurities and, in some cases, to penicillin itself (17, 116, 204, 252, 263, 273, 327, 332).

The allergic power of the amorphous calcium penicillin which was used later appeared to be somewhat greater than that of other salts, especially potassium, which was afterwards experimented with.

But what caused even more hypersensitiveness and reactions, was the addition, in order to prolong their action, of bee wax and peanut oil (114), mediums which, in spite of contrary opinions (144), proved sensitizing (51, 420).

Using crystalline penicillin immediately was followed by a diminishment of the reactions (425), which increased again when it was added to retarding agents such as sesame oil, etc. (74, 243, 244).

The substitution of procaine, determined a new diminution of allergic manifestations, but the continuous increase of the number of patients who have been submitted to repeated treatments with this antibiotic has brought about, once more, a relative increase of allergic reactions.

What has mostly contributed, has been the indiscriminate use of topical applications, instillations and ointments, which may provoke sensitizations although they often contain penicillin in insufficient doses to obtain therapeutic results (8).

With the object of setting aside these inconveniences, other compounds have been resorted to, such as penicillin O (allyl mercapto methyl penicillin), which so far has proved to be slightly less sensitizing (4, 413). It has also been associated with several antihistaminics ("hypoallergenic" penicillins) (210), which, although they do not lack sensitizing power, generally only provoke lessened reactions (251, 362, 363).

Most recent statistics show that allergic reactions appear in a 3-5 % (250, 318) proportion in patients who are given ordinary penicillin.

The hypersensitivity may be made manifest even with the

use of minimum doses of the antibiotic, but apparently appear easier when higher doses are given (244).

Penicillin may bring about reactions, whatever the methods of administration¹: topical, by aerosols², oral (196, 287), intramuscular and intrathecal (108, 194).

Of all the foregoing, the topical method, as with sulphonamides, appears to be the one which provokes sensitization with most frequent regularity.

The release of the reaction may be effected when employing a different method of administration than that which brought about the sensitization (25, 35, 101, 287, 404, 427).

In addition to this hypersensitiveness, provoked by its therapeutical application, this antibiotic may provoke allergy in those individuals who, due to their occupations, must handle it (physicians, chemists, nurses, workmen) (18, 35, 139, 267, 312, 360).

The development of the process of allergization varies from four days (277), in therapeutical topical applications, to several months (139, 267), in those persons who handle this product.

Once the sensitization has been brought about, the precipitating contact with the antibiotic may bring about the onset of the symptoms, either immediately or after several hours or days of application, or even with a considerable delay, once its administration has ceased (267, 408).

The immediate reactions appear generally in the form of urticaria, angioneurotic edema or serum-sickness, while the delayed ones are of an erythematovesicular or exfoliative type (228), but these relations, between the moment of the reaction and their nature, are far from being fixed in an absolute manner (91, 160, 192).

The most frequent allergic symptoms appear in the skin and the mucosae (99).

¹ 28, 31, 66, 73, 70, 117, 152, 153, 154, 196, 222, 257, 277, 288, 352, 412, 427, 435.

² 15, 152, 216, 241, 309, 361.

According to the method of administration¹, either a contact dermatitis may be started or, in the case of a systemic origin, urticaria² and angio-neurotic edema; pruritus (138, 196, 267); morbilliform, papular (370, 393), vesicular (76, 164, 196), purpuric (6, 310) and nodose (76) erythemas; ampullar (276, 393), exfoliative (118, 198, 234, 412), gangrenous (91) dermatosis, etc.

Dermal mycotic infectious exacerbations may also appear, either of a previous or existing nature (77, 228, 340, 393), or provoke the reaction only on a mycotic or bacterial "ides" level (187, 392).

In exceptional cases, the existence of photosensitization has been found (55, 107, 288, 393).

Sometimes the reactions appear in the respiratory system: acute rhinopathy (225, 267), glottic edema (7), asthma (146, 310), pulmonary infiltrations (124) and Loeffler's syndrome (114).

They may also be found in the renal system: nephritis with albuminuria and cylindruria (305, 372); or in the cerebro-spinal system; cerebral edema (226), convulsive (76) seizures and hallucinatory psychosis.

In other cases they reproduce the symptoms of the serum-sickness³ or anaphylactic (76, 78, 112, 194, 288) shock and they even, sometimes, result in death (236, 313, 416, 431).

The hemopathies caused by partial or total inhibitions of the hematopoietic system are very rare and usually consist in thrombocytopenia or agranulocytosis (370).

When the administration of penicillin is carried out by means of repeated injections, sterile abscesses sometime appear "in situ", attributable to local Arthus phenomena (53).

Finally, certain general symptoms of an undetermined nature, such as fever and migraine, have been attributed also to

¹ 18, 35, 139, 163, 257, 265, 267, 277, 288, 298, 312, 330, 343, 352, 360, 392, 393, 408.

² 72, 89, 100, 135, 147, 196, 219, 228, 230, 252, 271, 303, 338, 347, 379, 393, 412, 428, 430, 439.

³ 54, 160, 173, 220, 271, 299, 376, 378, 381, 400, 432.

the existence of allergy to the antibiotic (100, 146, 252, 271, 298, 305, 370).

ALLERGY TO STREPTOMYCIN

The therapeutical application of streptomycin may provoke allergic reactions. Sometimes these are limited to a plain eosinophilia (290) but, in other cases, they also acquire a clinical symptomatology, especially in the form of maculopapular (186, 190, 411, 441) and eczematous (336) eruptions which may, in some cases, even develop into exfoliative dermatitis (63, 180). In contrast to penicillin, urticaria is very rare (63).

On certain occasions arthralgias appear, but they are less frequent now due to the fact that purer preparations are being used (415).

We have also known of isolated cases of anaphylactic shocks (324) and of fatal aplastic anaemia (434).

Streptomycin produces manifestations of contact eczema in those persons who, due to their occupations, must handle it continuously. The characteristic eruption sometimes starts on the hands and, with less frequency, on the eyelids (317); and from there it may extend and even spread all over the body (5, 31, 63, 81, 111, 276, 342, 361, 364, 377, 385).

Hypersensitiveness to streptomycin is sometimes extreme: in the case of professional dermatosis, eruptions may appear by simply entering places where the drug is handled and the previously mentioned case of anaphylactic shock, followed an intradermal test carried out for diagnosis purposes.

ALLERGY TO CHLOROMYCETIN

Maculo-papular and polyform eruptions have appeared on patients who took the drug (29, 201, 404); and contact dermatitis, in a relatively small percentage, on those on whom a 10 % ointment of the antibiotic was applied (75, 323).

Certain oral and pharyngeal complications, consisting in glossitis, black tongue, pharyngitis, etc., are interpreted as in-

vasions of *monilia albicans*, subsequent to the disappearance of the bacterial flora habitual in the fauces, rather than as allergic reactions (433).

ALLERGY TO AUREOMYCIN AND TERRAMYCIN

Up to date, very few reactions have been attributable to the use of these antibiotics. They have consisted in cutaneous manifestations: urticaria, eruptions of a multiform type and eczema, that appeared in patients who took or used these antibiotics locally (150, 231, 296, 358).

The only comparative study known to us regarding the allergenic power of these new antibiotics, place them in the following decreasing order: Aureomycin, Terramycin and Chloromycetin (295).

DIAGNOSIS

The diagnosis of allergy to chemotherapics and antibiotics follow the same lines as the diagnosis of the other etiological forms of hypersensitivity (72, 177, 254, 284, 398, 403, 406, 461).

In the first place, the anamnesis reveals the paroxysmal and, in general, reversible character of those manifestations, together with its appearance after contact with the therapeutic agent.

In particularly favourable cases several similar episodes have taken place, sometimes of an increasing severity, which have ended by directing the patient's attention, who then correctly identifies the responsible agent.

In professional allergies, alternative remission and exacerbation of the symptoms following the interruption and resumption of work, are very significant.

The clinical examination reveals the existence of an urticarial or edematous dermatosis, rhinopathy, or asthma, whose probable allergic nature is already evident.

These diagnostic impressions are confirmed by the disappearance of the symptoms when stopping contact with the incriminating drug and, in certain special cases, by the possibility of provoking their reappearance on administering the drug again, taking great care to give exact measurements and administer minimum doses.

On the other hand, the possibilities of objective verification regarding hypersensitiveness are generally very scarce (146, 305, 393), although they increase somewhat in the case of contact dermatitis (120, 276, 336, 361, 364, 377, 385). In this latter instance, the tests that reproduce most faithfully the conditions in which the allergic processes have been developed, i.e. contact or patch tests, usually give positive results (271, 276, 364), moreover if they are carried out in cutaneous regions immediate to the place of the lesions (25, 118).

If the lesion results from photosensitization, the zone where the patch is fixed should be exposed to ultraviolet rays.

Only in exceptional cases, a contact dermatitis which has given a negative patch test, may give a positive skin reaction (429).

The conjunctival tests are constantly negative (228, 281).

Only when the allergic process results from the ingestion or injection of the drug may we recur to scratch and intradermal tests.

These tests are nearly always negative in the case of allergy to sulphonamides. In contrast, with streptomycin and penicillin (118, 271, 288) it is possible to obtain immediate or delayed positive reactions. The specific value of these is, however, subject to controversy.

When these tests are carried out with penicillin, 10,000 to 50,000 U. of crystalline penicillin, recently diluted, are generally used in the scratch test; and from $2\frac{1}{2}$ to 2,000 U. per tenth of cubic centimeter in the intradermal test. Several authors claim that, in the latter instance, it is necessary to use a higher concentration, i.e. 100 to 1,000 U. per hundredth of cubic centimeter.

In spite of some favourable opinions (191), we do not advise that intradermal tests with streptomycin be carried out, due to the danger involved, either in causing a violent reaction or in transforming the hypersensitiveness from local to general (361).

The passive transfer tests are generally negative (54, 146, 276, 327), due to the reduced amount of circulating antibodies, but in exceptional cases they may be positive (96, 397).

In order to set aside the insufficiency of the classical tests, principally with sulphonamides, certain special procedures have been employed. We have, thus, firstly tried patch testing and afterwards tried to precipitate the reaction through the ingestion of the drug. According to its author, this procedure assures positive results in the majority of cases of allergy to sulphonamides (302).

Another investigator has made healthy persons ingest sulphonamides, during a period of over 5 days, and later used their serum to carry out intradermal reactions in patients suspected of hypersensitiveness, and he affirms that he obtained immediate positive reactions (139). This opinion is, however, not generally accepted (126, 355).

There are others who report favourable results by means of an inverse procedure: they effect the passive transfer of the serum from the hypersensitive individuals, and inject it in healthy persons who have been taking sulphonamides for more than three days (185).

The extreme artificiality of these tests, their several steps, and the possibility of producing non-specific reactions, take away a lot of their probable practical value.

These disadvantages are also found in the precipitin-test, using the patient's serum, a method which has been supported by some experimentors (54).

TREATMENT

The treatment depends fundamentally on the type of reaction provoked by the drug and not by its nature, since there is no drug which can be called antagonistic to the effects of chemotherapeutics and antibiotics.

The general rules are as follows:

1. Immediate suppression of the drug, except when the reaction is very slight, or when the antibiotic cannot be dispensed with.
2. Symptomatic treatment.
3. Specific hyposensitization when this measure is necessary and possible.

The symptomatic therapy is similar to that of all allergic manifestations. It consists in the administration of sympathetomimetics: epinephrine (7, 160), ephedrine, etc.; aminophyllin, procaine (400), lobelin, etc.; in doses and by methods which are well-known.

Furthermore, non-specific hyposensitizing means are also employed; calcium and magnesium bromide salts, hyposulphites, auto-hemotherapy, etc.

Antihistaminics may be useful (213, 303, 389); their administration, by oral or parenteral means, in high doses, may sometimes calm some of the most troublesome symptoms, especially the pruritus, but they have proved of little value when the reactions are very intense (442).

As treatment of a general nature, the use of cortisone and especially of pituitary adrenocorticotrophin is indicated, but they must be reserved for serious cases and not used for slight or transitory reactions.

Since cutaneous lesions are the most frequent, we shall describe, with some detail, their therapy, in accordance with the clinical type:

a) *Vascular-edematous type* (Urticaria, Quincke's edema)

General treatment already laid down. The local treatment consists of the application of inert powders or aqueous pastes.

b) *Epithelial or eczematous type*

The general treatment is the same as the above. The benefit obtained from the use of antihistaminics is far less than that of the previous group.

As far as may be possible, exposure to intense light in the case of dermatitis due to drugs that may cause photosensitization (sulpha and penicillin) must be avoided.

The local treatment will depend on the intensity of the outbreak, as well as on its exudative character, which may be more or less intense. Active substances (ichthyol, sulphur, etc.) should be avoided, and preference given to lotions of weak astringent and antiseptic power, especially potassium permanganate of 0.25 per mil and lead subacetate of 1 or 2 % (white water of Codex). These medicaments are especially indicated in extensive and exudative lesions.

When the exudative character is less intense, pomades and aqueous pastes or calamine lotions, oil calcareous liniment, etc., should be used. The possible benefit given by antihistaminic pomades require further experience (361).

c) *Polymorphous and maculo-papular erythema type*

Generally they do not require an extensive treatment, since the outbreak is of short duration and spontaneously recedes. Antihistaminics should be used and light should be avoided.

d) *Generalized dermatitis, either exfoliative or vesiculo-edematous*

As we are dealing with reactions which may present serious danger, the maximum therapeutical precautions are necessary. The state of the excretory organs should be especially watched. The possibility of subsequent septic and escharotic complications should be borne in mind.

As drug of a general nature, in addition to the previously mentioned non-specific hyposensitizing means, ACTH and Cortisone should be used.

The external treatment is similar to that of the eczematous type.

Specific hyposensitization has been attempted in those cases where the administration of a chemotherapeutic or antibiotic was imperiously necessary—particularly, at first, when there was no possibility of substituting one for the other. With the sulphonamides it usually proved impossible. More success has been obtained with penicillin, but at present it is only employed in allergic persons who, due to their occupations, must continue using the drug.

Different methods have been suggested. One of them, similar to that employed with hay-fever, consists in injecting penicillin every other day, starting by a half unit dose and increasing it gradually until a tolerance to appreciable quantities of the antibiotic is attained (298).

Oral hyposensitization, by means of the ingestion of capsules containing 15,000 units, during a period of thirty days, has also proved successful in certain cases (288).

With streptomycin it is harder, if not impossible, to attain an adequate tolerance once the sensitization has been developed, for which reason it has been found necessary to take extreme prophylactic precautions in those persons who must handle the drug (276-361).

We have had no experience regarding the possibilities of hyposensitizing patients who are allergic to the new antibiotics; on the other hand, since the hypersensitivity does not appear to extend to all of them, there is always the possibility of returning to that which can be tolerated.

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